



Europäisches Patentamt
European Patent Office
Office européen des brevets



Publication number : **0 324 431 B1**

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification :
25.03.92 Bulletin 92/13

(51) Int. Cl.⁵ : **C07D 401/04, A61K 31/445**

(21) Application number : **89100332.9**

(22) Date of filing : **10.01.89**

(54) **New indolylpiperidine compounds, processes for the preparation thereof and pharmaceutical composition comprising the same.**

The file contains technical information submitted after the application was filed and not included in this specification

(30) Priority : **14.01.88 GB 8800795**
01.08.88 GB 8818260

(43) Date of publication of application :
19.07.89 Bulletin 89/29

(45) Publication of the grant of the patent :
25.03.92 Bulletin 92/13

(84) Designated Contracting States :
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited :
EP-A- 0 058 975
EP-A- 0 157 420

(73) Proprietor : **FUJISAWA PHARMACEUTICAL CO., LTD.**
3, Doshomachi 4-chome Higashi-ku
Osaka-shi Osaka 541 (JP)

(72) Inventor : **Matsuo, Masaaki**
2-1-619, Nakasakurazuka 5-chome
Toyonaka-shi Osaka 560 (JP)
Inventor : **Manabe, Takashi**
8-2, Tokiwadai 3-chome Toyono-cho
Toyono-gun Osaka 563-01 (JP)
Inventor : **Shigenaga, Shinji**
2-503-803, Minamiochiai 2-chome Suma-ku
Kobe-shi Hyogo 654-01 (JP)
Inventor : **Matsuda, Hiroshi**
3-3, Mitsuyanaka 2-chome Yodogawa-ku
Osaka-shi Osaka 532 (JP)

(74) Representative : **Türk, Gille, Hrabal**
Brucknerstrasse 20
W-4000 Düsseldorf 13 (DE)

EP 0 324 431 B1

Note : Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

Description

This invention relates to new indolylpiperidine compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new indolylpiperidine compounds and pharmaceutically acceptable salt thereof which have antiallergic activity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the treatment of allergic disease in human beings or animals.

One object of this invention is to provide new indolylpiperidine compounds and pharmaceutically acceptable salts thereof which possess antiallergic activity.

Another object of this invention is to provide processes for the preparation of said indolylpiperidine compounds or salts thereof.

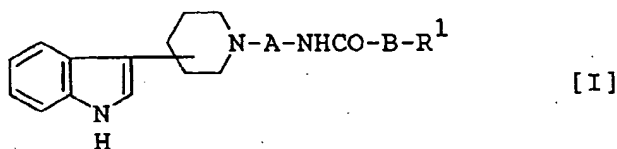
A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said indolylpiperidine compounds or pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment of allergic disease such as allergic asthma, allergic rhinitis, allergic conjunctivitis, chronic urticaria in human beings or animals.

Some indolylpiperidine compounds having anti-allergic activity have been known as described in British Patent Application Publication No. 2093455.

Some amide derivatives having anti-allergic activity have been known as described in European Patent Application Publication No. 157420.

The object indolylpiperidine compounds of this invention are new and can be represented by the following general formula [I]:



wherein

R¹ is phenyl substituted with substituent(s) selected from the group consisting of hydroxy, C₁-C₆ alkoxy, (C₁-C₆)alkoxy-(C₁-C₆)alkoxy, C₁-C₆ alkyl, C₁-C₆ alkanoyloxy, C₁-C₆ alkoxy-carbonyloxy, halogen and C₁-C₆ alkoxy,

A is C₁-C₆ alkylene, and

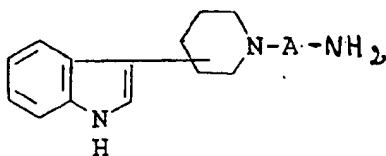
B is vinylene, propenylene, butenylene, pentenylene, butadienylene or pentadienylene.

The object compound [I] or its salt can be prepared by processes as illustrated in the following reaction schemes.

Process 1

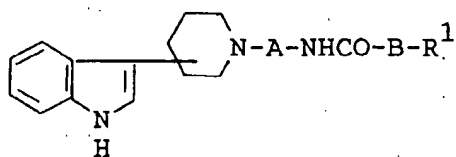


or its reactive derivative
at the carboxy group or
a salt thereof



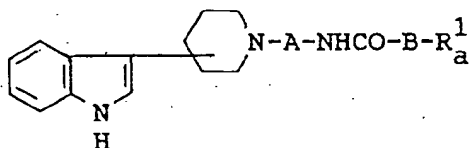
[II]

or its reactive derivative
at the amino group or
a salt thereof



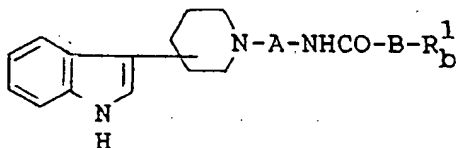
[I]
or its salt

Process 2



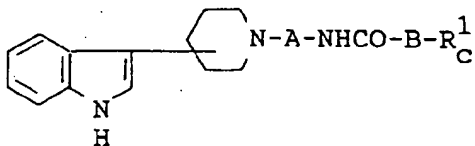
Elimination of C₁-C₆ alkoxy-
(C₁-C₆)alkoxy(C₁-C₆)alkyl

[Ia]
or its salt



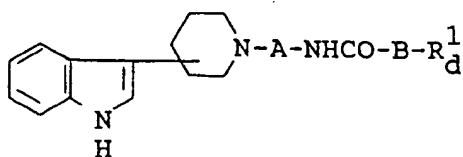
[Ib]
or its salt

Process 3



Acylation

[Ic]
or its salt



[Id]

or its salt

wherein

R_a^1 is phenyl substituted with C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy, with C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy and halogen, with

C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy and C_1 - C_6 alkyl, or with C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy and C_1 - C_6 alkoxy,

R_b^1 is phenyl substituted with hydroxy, with hydroxy and halogen, with hydroxy and C_1 - C_6 alkyl, or with hydroxy and C_1 - C_6 alkoxy,

R_c^1 is phenyl substituted with hydroxy, or with hydroxy and C_1 - C_6 alkoxy,

R_d^1 is phenyl substituted with C_1 - C_6 alkoxycarbonyloxy, or with acyloxy selected from C_1 - C_6 alkanoyloxy and C_1 - C_6 alkoxycarbonyloxy and C_1 - C_6 alkoxy, and

R^1 , A and B are each as defined above.

In the above and subsequent descriptions of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

Suitable " C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy" may be methoxyethoxymethoxy.

Suitable " C_1 - C_6 alkanoyloxy" may be formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy, hexanoyloxy, 3,3-dimethylbutyryloxy.

Suitable " C_1 - C_6 alkoxycarbonyloxy" may be methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, tert-butoxycarbonyloxy, pentyloxycarbonyloxy, hexyloxycarbonyloxy.

Suitable "halogen" is fluorine, chlorine, bromine and iodine.

Suitable "acyloxy" may be selected from C_1 - C_6 alkanoyloxy and C_1 - C_6 alkoxycarbonyloxy as above-mentioned.

Suitable " C_1 - C_6 alkoxy" may be a straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy in which the preferable one is C_1 - C_4 alkoxy and the most preferable one is methoxy.

Preferable example of "phenyl substituted with substituent(s) selected from the group consisting of hydroxy, C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy, C_1 - C_6 alkyl, C_1 - C_6 alkanoyloxy, C_1 - C_6 alkoxycarbonyloxy, halogen and C_1 - C_6 alkoxy" may be mono-, or di-, or trihydroxyphenyl; mono-, or di-, or tri(halo)phenyl [e.g. chlorophenyl, fluorophenyl, dichlorophenyl, trifluorophenyl]; mono-, or di-, or tri(C_1 - C_6)alkylphenyl [e.g. tolyl, mesityl, cumenyl, xylol, ethylphenyl, diethylphenyl, isopropylphenyl, diisopropylphenyl, di-tert-butylphenyl]; mono-, or di-, or tri(C_1 - C_6)alkoxyphenyl [e.g. methoxyphenyl, ethoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, diethoxyphenyl, diisopropoxyphenyl]; mono-, or dihydroxy and mono-, or di(C_1 - C_6)alkoxy substituted phenyl [e.g. methoxy(hydroxy)phenyl, ethoxy(hydroxy)phenyl, isopropoxy(hydroxy)phenyl, dimethoxy(hydroxy)phenyl, diethoxy(hydroxy)phenyl, diisopropoxy(hydroxy)phenyl, methoxy(dihydroxy)phenyl, methoxy(ethoxy)hydroxyphenyl]; mono-, or dihydroxy and mono-, or di(C_1 - C_6)alkyl substituted phenyl [e.g. methyl(hydroxy)phenyl, ethyl(hydroxy)phenyl, propyl(hydroxy)phenyl, isopropyl(hydroxy)phenyl, dimethyl(hydroxy)phenyl, diethyl(hydroxy)phenyl, diisopropyl(hydroxy)phenyl, di-tert-butyl(hydroxy)phenyl, methyl(dihydroxy)phenyl, methyl(ethyl)hydroxyphenyl]; mono-, or dihydroxy and mono-, or dihalo substituted phenyl [e.g. chloro(hydroxy)phenyl, dichloro(hydroxy)phenyl, fluoro(hydroxy)phenyl, chloro(dihydroxy)phenyl]; mono-, or di-, or tri(C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy)phenyl [e.g. mono-, or di-, or tri(methoxyethoxymethoxy)phenyl]; mono-, or di-, or tri(C_1 - C_6)alkanoyloxyphenyl [e.g. formyloxyphenyl, acetyloxyphenyl, propionyloxyphenyl, diacetyloxyphenyl, dipropionyloxyphenyl, triacetyloxyphenyl]; mono-, or di-, or tri(C_1 - C_6)alkoxycarbonyloxyphenyl [e.g. methoxycarbonyloxyphenyl, ethoxycarbonyloxyphenyl, diethoxycarbonyloxyphenyl, triethoxycarbonyloxyphenyl]; mono-, or di(C_1 - C_6)alkoxy and mono-, or di(C_1 - C_6 alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy)substituted phenyl [e.g. methoxy(methoxyethoxymethoxy)phenyl, ethoxy(methoxyethoxymethoxy)phenyl, dimethoxy(methoxyethoxymethoxy)phenyl, diethoxy(methoxyethoxymethoxy)phenyl,

diisopropoxy(methoxyethoxymethoxy)phenyl]; mono-, or di(C₁-C₆)alkanoyloxy and mono-, or di(C₁-C₆)alkoxy substituted phenyl [e.g. acetyloxy(methoxy)phenyl, propionyloxy(methoxy)phenyl, acetyloxy(ethoxy)phenyl, acetyloxy(dimethoxy)phenyl, propionyloxy(dimethoxy)phenyl, acetyloxy(diethoxy)phenyl, acetyloxy(diisopropoxy)phenyl, diacetyloxy(methoxy)phenyl]; mono-, or di(C₁-C₆)alkoxycarbonyloxy and mono-, or di(C₁-C₆)alkoxy substituted phenyl [e.g. methoxycarbonyloxy(methoxy)phenyl, ethoxycarbonyloxy(methoxy)phenyl, ethoxycarbonyloxy(ethoxy)phenyl, methoxycarbonyloxy(dimethoxy)phenyl, ethoxycarbonyloxy(dimethoxy)phenyl, ethoxycarbonyloxy(diethoxy)phenyl, ethoxycarbonyloxy(diisopropoxy)phenyl]; mono-, or di(C₁-C₆)alkyl and mono-, or di[C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy] substituted phenyl [e.g. methyl(methoxyethoxymethoxy)phenyl, ethyl(methoxyethoxymethoxy)phenyl, dimethyl(methoxyethoxymethoxy)phenyl, diethyl(methoxyethoxymethoxy)phenyl, diisopropyl(methoxyethoxymethoxy)phenyl, di-tert-butyl(methoxyethoxymethoxy)phenyl]; mono-, or di(C₁-C₆)alkanoyloxy and mono-, or di(C₁-C₆)alkyl substituted phenyl [e.g. acetyloxy(methyl)phenyl, propionyloxy(methyl)phenyl, acetyloxy(ethyl)phenyl, acetyloxy(dimethyl)phenyl, propionyloxy(dimethyl)phenyl, acetyloxy(diethyl)phenyl, acetyloxy(diisopropyl)phenyl, diacetyloxy(methyl)phenyl]; mono-, or di(C₁-C₆)alkoxycarbonyloxy and mono-, or di(C₁-C₆)alkyl substituted phenyl [e.g. methoxycarbonyloxy(methyl)phenyl, ethoxycarbonyloxy(methyl)phenyl, ethoxycarbonyloxy(ethyl)phenyl, methoxycarbonyloxy(dimethyl)phenyl, ethoxycarbonyloxy(dimethyl)phenyl, ethoxycarbonyloxy(diethyl)phenyl, ethoxycarbonyloxy(diisopropyl)phenyl]; mono-, or dihalo and mono-, or di[C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy]substituted phenyl [e.g. chloro(methoxyethoxymethoxy)phenyl, dichloro(methoxyethoxymethoxy)phenyl, fluoro(methoxyethoxymethoxy)phenyl]; mono-, or di(C₁-C₆)alkanoyloxy and mono-, or dihalo substituted phenyl [e.g. acetyloxy(chloro)phenyl, propionyloxy(chloro)phenyl, acetyloxy(dichloro)phenyl]; and mono-, or di(C₁-C₆)alkoxycarbonyloxy and mono-, or dihalo substituted phenyl [e.g. methoxycarbonyloxy(chloro)phenyl, ethoxycarbonyloxy(chloro)phenyl, ethoxycarbonyloxy(dichloro)phenyl].

Preferable examples of "phenyl substituted with C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, with C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy and halogen, or with C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy and C₁-C₆ alkoxy" may be the same as above-mentioned mono-, or di-, or tri[C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy]phenyl; mono-, or dihalo and mono-, or di[C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy]substituted phenyl; mono-, or di(C₁-C₆)alkoxy and mono-, or di[C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy] substituted phenyl; and mono-, or di(C₁-C₆)alkyl and mono-, or di[C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy]substituted phenyl.

Preferable example of "phenyl substituted with hydroxy, with hydroxy and halogen, with hydroxy and C₁-C₆ alkyl, or with hydroxy and C₁-C₆ alkoxy" may be the same as above-mentioned mono-, or di-, or trihydroxy phenyl; mono-, or dihydroxy and mono-, or dihalo substituted phenyl; mono-, or dihydroxy and mono-, or di(C₁-C₆)alkoxy substituted phenyl; and mono-, or dihydroxy and mono-, or di(C₁-C₆)alkyl substituted phenyl.

Preferable examples of "phenyl substituted with C₁-C₆ alkoxycarbonyloxy, or with acyloxy selected from C₁-C₆ alkanoyloxy and C₁-C₆ alkoxycarbonyloxy and C₁-C₆ alkoxy" may be the same as above-mentioned mono-, or di-, or tri(C₁-C₆)alkoxycarbonyloxyphenyl; mono-, or di(C₁-C₆)alkanoyloxy and mono-, or di(C₁-C₆)alkoxy substituted phenyl; and mono- or di(C₁-C₆)alkoxycarbonyloxy and mono- or di(C₁-C₆)alkoxy substituted phenyl.

Suitable "C₁-C₆ alkylene" may be, a straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, ethylethylene, propylene, pentamethylene, hexamethylene.

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt], an acid addition salt such as an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt].

With respect to the salts of the compounds [Ia], [Ib], [Ic] and [Id] in the Processes 2 and 3, it is to be noted that these compounds are included within the scope of the compound [I], and accordingly the suitable examples of the salts of these compounds are to be referred to those as exemplified for the object compound [I].

The processes for preparing the object compounds [I] of the present invention are explained in detail in the following.

Process 1

The object compound [I] or its salt can be prepared by reacting a compound [II] or its reactive derivative at the amino group or a salt thereof with a compound [III] or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound [II] may include Schiff's base type imino

or its tautomeric enamine type isomer formed by the reaction of the compound [II] with a carbonyl compound such as aldehyde, ketone; a silyl derivative formed by the reaction of the compound [II] with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea; a derivative formed by reaction of the compound [II] with phosphorus trichloride or phosgene.

Suitable salts of the compound [II] and its reactive derivative can be referred to the acid addition salt as exemplified for the compound [I].

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide, an activated ester. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid] or aromatic carboxylic acid [e.g. benzoic acid]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranil ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester], or an ester with an N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole].

These reactive derivatives can optionally be selected from them according to the kind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, potassium salt], an alkaline earth metal salt [e.g. calcium salt, magnesium salt], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water. In this reaction, when the compound [III] is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; diphenylphosphinic chloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate]; triphenylphosphine; 2-ethyl-7-hydroxybenzoxazolium salt; 2-ethyl-5-(m-sulfohenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 2

The compound [Ib] or its salt can be prepared by subjecting a compound [Ia] or its salt to elimination reaction of C_1-C_6 alkoxy(C_1-C_6)alkoxy(C_1-C_6)alkyl.

This reaction is carried out in accordance with a conventional method such as hydrolysis.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium], an alkaline earth metal [e.g. magnesium calcium], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine], picoline 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid,

trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride].

The elimination using trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid] is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol], methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 3

The object compound [Id] or its salt can be prepared by reacting a compound [Ic] or its salt with an acylating agent.

Suitable acylating agents are the corresponding carboxylic acid, which are represented by the formula : R^2-OH wherein R^2 is acyl, and reactive derivatives thereof.

Suitable "acyl" may be the same as acyl group for "acyloxy" as exemplified above.

Suitable said reactive derivatives can be referred to the ones at the carboxy groups of the compound [III] as exemplified above. The kind of such reactive derivatives can be selected depending on the kind of acyl group to be introduced.

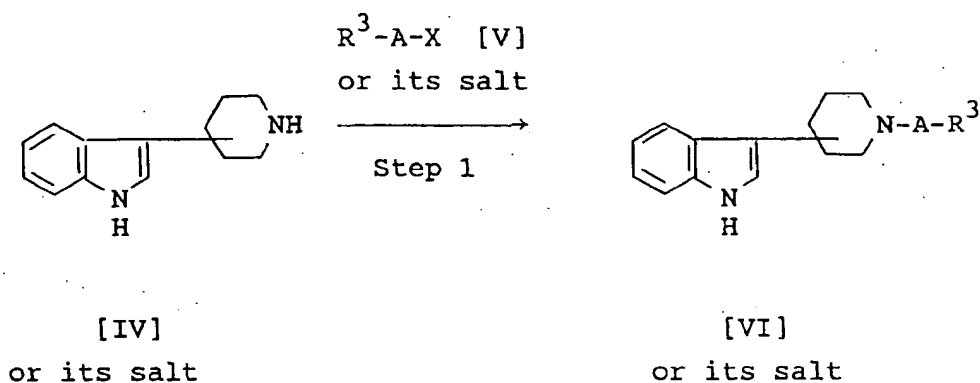
The reaction is usually carried out in a conventional solvent, such as methylene chloride, chloroform, benzene, toluene, pyridine, diethyl ether, dioxane, tetrahydrofuran, acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide or any other organic solvent which does not adversely affect the reaction. In case that the acylating agent is liquid, it can also be used as a solvent. In case that the carboxylic acid compounds are used as acylating agent in the free acid form or salt form, it is preferable to carry out the reaction in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide.

The reaction temperature is not critical and the reaction can be carried out under cooling, at ambient temperature, or under heating.

This reaction is preferably carried out in the presence of an inorganic base, for example an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, or an alkali metal carbonate or hydrogen carbonate such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate, or in the presence of an organic base, for example a tertiary amine such as triethylamine, pyridine, N-methylmorpholine or N,N-dimethylaniline.

Among the starting compounds [II] and [III], some of them are new and can be prepared by processes as illustrated in the following reaction schemes

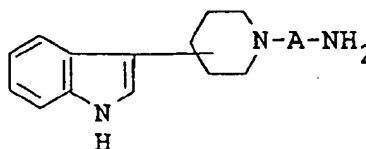
Process A



Elimination of the
amino-protective group

5

Step 2



[II]

or its salt

10

Process B

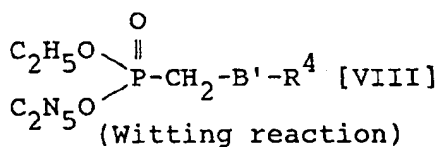
15

20

R^1 -CHO

[VII]

or its salt



Step 1

R^1 -CH=CH-B'-R⁴

[IX]

or its salt

25

Elimination of the
carboxy-protective
group

30

Step 2

R^1 -CH=CH-B'-COOH

[IIIa]

or its salt

35

wherein

R³ is protected amino,

R⁴ is protected carboxy,

B' is methylene, ethylene, trimethylene, vinylene or propenylene,

X is a leaving group,

40

R¹ and A are each as defined above.

Suitable "protected amino" may be acylamino such as substituted or unsubstituted C₁-C₆ alkanoylamino [e.g. formylamino, acetylamino, propionylamino, trifluoroacetylamino], phthaloylimino, C₁-C₆ alkoxy-carbonylamino [e.g. tert-butoxycarbonylamino, tert-amylloxycarbonylamino], substituted or unsubstituted aralkyloxycarbonylamino [e.g. benzyloxycarbonylamino, p-nitrobenzyloxycarbonylamino], substituted or

45

unsubstituted arenesulfonylamino [e.g. benzenesulfonylamino, tosylamino], nitrophenylsulfonylamino, aralkylamino [e.g. tritylamino, benzylamino, etc.].

Suitable "protected carboxy" may be carboxy group protected by conventional protective group such as C₁-C₆ alkoxy-carbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, neopentyloxycarbonyl, hexyloxycarbonyl], optionally substituted ar(C₁-C₆)alkoxy-carbonyl for example, mono or di or triphenyl(C₁-C₆)alkoxy-carbonyl which may be substituted with nitro [e.g. benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl].

50

Suitable "leaving group" may be an acid residue such as halogen [e.g. chlorine, bromine, fluorine and iodine], sulfonyloxy [e.g. mesyloxy, tosyloxy, phenylsulfonyloxy].

55

The processes for preparing the starting compounds are explained in detail in the following.

Process AStep 1

5 The compound [VI] or its salt can be prepared by reacting a compound [IV] or its salt with a compound [V] or its salt.

Suitable salts of the compounds [IV], [V] and [VI] can be referred to the acid addition salts as exemplified for the compound [I].

10 This reaction is usually carried out in a conventional solvent such as water, an alcohol [e.g. methanol, ethanol, isopropyl alcohol], dioxane, tetrahydrofuran, N,N-dimethylformamide, methylene chloride, chloroform, tetrachloromethane, or any other conventional solvent which does not adversely affect this reaction, or a mixture thereof.

The reaction is carried out at ambient temperature, under warming or under heating, although the reaction temperature is not critical.

15 This reaction can also be conducted in the presence of an inorganic base, for example an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, or an alkali metal carbonate or hydrogen carbonate such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate, or in the presence of an organic base, for example a tertiary amine such as triethylamine, pyridine or N,N-dimethylaniline.

20 This reaction can also be performed in the presence of an alkali metal halide such as sodium iodide or potassium iodide.

Step 2

25 The compound [II] or its salt can be prepared by subjecting a compound [VI] or its salt to elimination reaction of the amino-protective group.

This elimination reaction can be carried out by a conventional manner, and the reaction mode [e.g. hydrolysis, reduction] and the reaction conditions [e.g. acid, base, catalyst, solvent, reaction temperature] of this reaction can be referred to those of the conventional elimination reaction of the amino-protective group.

30

Process BStep 1

35 The compound [IX] or its salt can be prepared by reacting a compound [VII] or its salt with a compound [VIII].

Suitable salts of the compounds [VII] and [IX] can be referred to the ones as exemplified for the compound [III].

40 This reaction is so-called Witting reaction, and the reaction mode and reaction conditions can be referred to those of the conventional Witting reaction.

Step 2

45 The compound [III] or its salt can be prepared by subjecting a compound [VIII] or its salt to elimination reaction of the carboxy-protective group.

This elimination reaction can be carried out by a conventional manner, and the reaction mode [e.g. hydrolysis, reduction] and the reaction conditions [e.g. acid, base, catalyst, solvent, reaction temperature] of this reaction can be referred to those of the conventional elimination reaction of the carboxy protective group.

50 The compounds obtained by the above Processes 1, 2, 3, A and B can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation.

It is to be noted that each of the object compound [I] and the starting compounds may include one or more stereoisomer due to asymmetric carbon atom(s) and/or carbon-carbon double bond (i.e. Z-isomer and E-isomer), and all such isomers and mixture thereof are included within the scope of this invention.

55 The new indolylpiperidine compound [I] and pharmaceutically acceptable salts thereof possess antiallergic activity and are useful for a therapeutic treatment or prophylaxis of allergic disease such as allergic asthma, allergic rhinitis, allergic conjunctivitis, chronic urticaria.

The compound [I] and a pharmaceutically acceptable salt thereof of this invention can be used in the form of conventional solid, semisolid or liquid pharmaceutical preparations in admixture with conventional organic

or inorganic carriers or excipients suitable for oral, parenteral or external application. The active ingredients may be affixed with conventional, nontoxic, pharmaceutically acceptable carriers having the form of, for example, tablets, pellets, capsules, patches, suppositories, solutions, emulsions or suspensions or any other form suitable for use. Usable carriers are not limited to any particular species. Thus, conventional carriers such as water, glucose, lactose, gum arabic, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch and urea and other carriers suitable for the manufacture of solid, semisolid or liquid preparations can be used. Furthermore, auxiliaries, stabilizers, thickening agents and colorants as well as aromas may be added.

The dose or therapeutically effective amount of the object compounds [I] of this invention may vary depending on the age and symptoms of each individual patient to be treated. Generally, the active ingredients are administered for disease treatment in a daily dose of about 0.1-100 mg/kg, preferably 0.1-10 mg/kg.

In order to illustrate the usefulness of the object compound [I], the pharmacological test data of some representative compounds of the compound [I] are shown in the following.

15 Test Compounds

Compound A : 1-[4-{5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}butyl]-4-(3-indolyl)-piperidine

Compound B : 1-[2-{5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)-piperidine

Compound C : 1-[2-{5-(4-Hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine

Compound D : 1-[2-{5-(4-Acetoxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)-piperidine

Compound E : 1-[2-{5-(4-Acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine

Compound F : 1-[2-{5-(3,5-Dichloro-4-hydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine

30 Test 1

Antagonistic action on anaphylactic asthma in guinea pigs

Male Hartley-strain guinea pigs weighing 305-400 g were used. These animals were sensitized by intravenous injection of 0.5 ml/animal of rabbit antiserum to egg-white albumin (PCA antibody titer 4,000). After 24 hours, the animals were housed individually in 5.3-liter plastic chambers. Using a commercial sprayer, a 5% egg-white albumin solution was sprayed in the form of an aerosol into each chamber at a rate of 0.16 ml/min for 2 minutes. Thirty minutes prior to the spraying of the egg-white albumin solution, the test compound was administered orally in varied concentrations. Each dosed group consisted of 5 animals. The prophylactic effect to anaphylaxis was expressed in terms of the ED₅₀ value determined on the basis of the number of guinea pigs which has survived for not less than 2 hours after antigen spraying for each administration concentration of the test compound. The values thus obtained are given in the following table.

Test Results

Test Compound	Prophylactic Effect ED ₅₀ (mg/kg)
A	0.5
C	0.5

Test 2

Anti-SRS-A activity

Peritoneal exudate cells were collected from glycogen-injected SD rats and adjusted to 1×10^7 cells/ml with Tyrode's solution. One milliliter of the cell suspension was incubated with indomethacin (10 µg/ml) and

each varied concentration of the test compound for 10 minutes and, then, further incubated with Ca^{++} -ionophore (A23187, 1 $\mu\text{g/ml}$) for 10 minutes. The supernatant was collected by centrifugation and the SRS-A (slow-reacting substance of anaphylaxis) activity was determined in terms of contractility of the isolated guinea pig ileum in the presence of mepyramine, atropine and methysergide.

5 The results were expressed in terms of the 50% inhibitory concentration to SRS-A synthesis or release from peritoneal exudate cells.

Test Results

10

Test Compound	Inhibitory Concentration IC_{50} ($\mu\text{g/ml}$)
B	0.91
C	0.68
D	0.6
E	0.23
F	0.65

15

20

25

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

30

A mixture of 4-(3-indolyl)piperidine (7.88 g), N-(2-bromoethyl)phthalimide (10.0 g) and sodium hydrogen carbonate (3.64 g) in dry N,N-dimethylformamide (93 ml) was heated at 68-74°C for 4 hours. After cooling, the reaction mixture was poured into ice-water (1,000 ml). The resulting precipitate was collected by filtration and washed with methanol to give 1-(2-phthalimidoethyl)-4-(3-indolyl)piperidine (5.53 g).

35 NMR ($\text{DMSO}-d_6$, δ) : 1.3-3.4 (11H, m), 3.77 (2H, t, $J=6.0\text{Hz}$), 6.8-7.8 (5H, m), 7.89 (4H, m), 10.73 (1H, s)

MASS : 373 (M^+), 213

Preparation 2

40

A mixture of 4-(3-indolyl)piperidine (7.47 g), N-(3-bromopropyl)phthalimide (10.0 g) and sodium hydrogen carbonate (3.45 g) in dry N,N-dimethylformamide (88 ml) was heated at 70°C for 2 hours. After cooling, the reaction mixture was poured into water (880 ml) and extracted with a mixture of chloroform and methanol (10:1, V/V). The organic layer was washed with a saturated sodium chloride solution and dried over magnesium sulfate. The solvent was distilled off and the residue was subjected to column chromatography on silica gel (290 g) and eluted with a mixture of chloroform and methanol (20:1, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure. The residue was triturated with diethyl ether to give pale yellow crystals of 1-(3-phthalimidopropyl)-4-(3-indolyl)-piperidine (5.83 g).

45 IR (Nujol) : 3360, 1770, 1704, 1040, 735, 712 cm^{-1}
 50 NMR ($\text{DMSO}-d_6$, δ) : 1.0-3.1 (13H, m), 3.67 (2H, t, $J=6.0\text{Hz}$), 6.8-7.6 (5H, m), 7.6-8.0 (4H, m), 10.63 (1H, s)

Preparation 3

55 1-(4-Phthalimidobutyl)-4-(3-indolyl)piperidine was obtained according to a similar manner to that of Preparation 2.

IR (Nujol) : 3400-3300 (broad), 1770, 1700 (broad) cm^{-1}

Preparation 4

A mixture of 1-(2-phthalimidoethyl)-4-(3-indolyl)-piperidine (6.3 g) and hydrazine monohydrate (2.2 g) in ethanol (250 ml) was refluxed for 70 minutes. After cooling, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was treated with 5% sodium hydroxide solution (300 ml) and extracted with ethyl acetate (300 ml). The organic layer was washed with a saturated sodium chloride solution and dried over magnesium sulfate. The evaporation of solvent gave 1-(2-aminoethyl)-4-(3-indolyl)piperidine (3.74 g).

IR (Nujol) : 3350, 1596, 953, 733 cm^{-1}
 NMR (CDCl_3 , δ) : 1.5-3.4 (15H, m), 6.8-7.8 (5H, m), 8.5 (1H, br s)
 MASS : 243 (M^+), 213

Preparation 5

The following compounds were obtained according to a similar manner to that of Preparation 4.

(1) 1-(3-Aminopropyl)-4-(3-indolyl)piperidine

IR (Nujol) : 3360, 3150, 1377, 1225 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.3-3.2 (17H, m), 6.7-7.7 (5H, m), 10.67 (1H, s)

(2) 1-(4-Aminobutyl)-4-(3-indolyl)piperidine

IR (Nujol) : 3390, 3150, 1110, 897, 736 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.0-3.2 (19H, m), 6.7-7.6 (5H, m), 10.67 (1H, s)

Preparation 6

A mixture of 4-hydroxy-3,5-dimethylbenzaldehyde (5 g), N,N-diisopropylethylamine (6.9 ml), (2-methoxyethoxy)methylchloride (4.26 ml) and 1,2-dichloroethane (65 ml) was refluxed for 5 hours. The reaction mixture was washed with water and dried over magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel and eluted with a mixture of n-hexane and ethyl acetate (8:2, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure to give 4-[(2-methoxyethoxy)methoxy]-3,5-dimethylbenzaldehyde (6.54 g).

IR (Neat) : 2900, 1690, 1600, 1130, 1100, 960, 740 cm^{-1}
 NMR (CDCl_3 , δ) : 2.30 (6H, s), 3.32 (3H, s), 3.75, 4.0 (each 2H, m), 5.19 (2H, m), 7.60 (2H, s), 9.93 (1H, s)

Preparation 7

The following compounds were obtained according to a similar manner to that of Preparation 6.

(1) 3,5-Diisopropyl-4-[(2-methoxyethoxy)methoxy]-benzaldehyde

IR (Nujol) : 2950, 1690, 1595, 1585, 955 cm^{-1}

(2) 4-[(2-Methoxyethoxy)methoxy]-3-methylbenzaldehyde

IR (Neat) : 2950, 1690, 1600, 1590, 980 cm^{-1}

NMR (CDCl_3 , δ) : 2.31 (3H, s), 3.38 (3H, s), 3.6, 3.8 (each 2H, m), 5.41 (2H, s), 7.15-7.85 (3H, m), 9.90 (1H, s)

(3) 3-Chloro-4-[(2-methoxyethoxy)methoxy]benzaldehyde

IR (Neat) : 1700, 1595, 1570, 950 cm^{-1}

NMR (CDCl_3 , δ) : 3.30 (3H, m), 3.6, 3.8 (each 2H, m), 5.53 (2H, s), 7.2-7.9 (3H, m), 9.88 (1H, s)

(4) 3,5-Dichloro-4-[(2-methoxyethoxy)methoxy]benzaldehyde

IR (Neat) : 2900, 1705, 1590, 1560, 920, 810 cm^{-1}

NMR (CDCl_3 , δ) : 3.4 (3H, s), 3.6, 4.1 (each 2H, m), 5.38 (2H, s), 7.82 (2H, s), 9.85 (1H, s)

(5) 3-Methoxy-2-[(2-methoxyethoxy)methoxy]benzaldehyde

IR (Neat) : 1690, 1585, 950, 850, 785, 750 cm^{-1}

NMR (CDCl_3 , δ) : 3.40 (3H, s), 3.6, 3.9 (each 2H, m), 3.95 (3H, s), 5.38 (2H, s), 7.2-7.6 (3H, m), 10.53 (1H, s)

MASS (m/e) : 240 (M^+), 89, 59

(6) 3,5-Di-tert-butyl-4-[(2-methoxyethoxy)methoxy]-benzaldehyde

IR (Neat) : 1695, 1595, 945 cm^{-1}

Preparation 8

To a stirred suspension of 60% sodium hydride (1.01 g) in dry tetrahydrofuran (60 ml), 80% triethyl 4-phosphonocrotonate (6.57 g) was added dropwise below 10°C under an inert atmosphere. After being stirred for 30 minutes, a solution of 4-[(2-methoxyethoxy)methoxy]-3,5-dimethylbenzaldehyde (5.0 g) in dry tetrahydrofuran (50 ml) was added thereto below 10°C. After stirring for 2 hours, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 ml), washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. The solvent was distilled off and the residue was subjected to column chromatography on silica gel (130 g) and eluted with a mixture of n-hexane and ethyl acetate (7:3, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure to give a syrup of ethyl 5-[4-[(2-methoxyethoxy)methoxy]-3,5-dimethylphenyl]-(2E,4E)-2,4-pentadienoate (5.28 g).

IR (Neat) : 2950, 1710, 1620, 1600, 970, 865 cm⁻¹

15 Preparation 9

The following compounds were obtained according to a similar manner to that of Preparation 8.

(1) Ethyl 5-[3,5-diisopropyl-4-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pentadienoate

IR (Nujol) : 1710, 1625, 1595, 965, 870 cm⁻¹

20 NMR (CDCl₃, δ) : 1.25 (12H, d, J=8Hz), 1.31 (3H, t, J=8Hz), 3.45 (2H, sextet, J=8Hz), 3.43 (3H, s), 3.7, 4.0 (each 2H, m), 4.25 (2H, q, J=8Hz), 5.03 (2H, s), 6.0 (1H, d, J=15Hz), 6.8-7.7 (5H, m)

MASS (m/e) : 362 (M⁺), 89, 59 (base)

(2) -Ethyl 5-[4-[(2-methoxyethoxy)methoxy]-3-methylphenyl]-(2E,4E)-2,4-pentadienoate

25 NMR (CDCl₃, δ) : 1.31 (3H, t, J=8Hz), 2.25 (3H, s), 3.35 (3H, s), 3.7, 3.9 (each 2H, m), 4.25 (2H, q, J=8Hz), 5.31 (2H, s), 5.95 (1H, d, J=15Hz), 6.7-7.7 (6H, m)

MASS (m/e) : 320 (M⁺), 276, 89, 59

(3) Ethyl 5-[3-chloro-4-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pentadienoate

IR (Neat) : 2900, 1710, 1630, 1600, 1055, 980 cm⁻¹

30 NMR (CDCl₃, δ) : 1.31 (3H, t, J=8Hz), 3.35 (3H, s), 3.7, 3.9 (each 2H, m), 4.28 (2H, q, J=8Hz), 5.33 (2H, s), 5.97 (1H, d, J=15Hz), 6.7-7.7 (6H, m)

(4) Ethyl 5-[3,5-dichloro-4-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pentadienoate

mp : 67-69°C (recrystallized from a mixture of toluene and ethyl acetate (8:1))

IR (Nujol) : 1710, 1630, 1545, 1000, 925, 860, 800 cm⁻¹

35 NMR (CDCl₃, δ) : 1.30 (3H, t, J=8Hz), 3.38 (3H, s), 3.6, 4.1 (each 2H, m), 4.23 (2H, q, J=8Hz), 5.29 (2H, s), 6.03 (1H, d, J=15Hz), 6.6-7.7 (5H, m)

MASS (m/e) : 376 (M+2), 375 (M+1), 374 (M⁺), 89 (base)

(5) Ethyl 5-[3-methoxy-2-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pentadienoate

mp : 48-49°C (recrystallized from a mixture of n-hexane and diisopropyl ether)

IR (Nujol) : 1720, 1623, 1000, 945, 850 cm⁻¹

40 NMR (CDCl₃, δ) : 1.35 (3H, t, J=7Hz), 3.4 (3H, s), 3.6, 3.9 (each 2H, m), 3.86 (3H, s), 4.27 (2H, q, J=7Hz), 5.25 (2H, s), 6.03 (1H, d, J=15Hz), 6.6-7.7 (6H, m)

(6) Ethyl 5-[4-methoxy-3-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pentadienoate

IR (Neat) : 1710, 1625, 1600, 1000 cm⁻¹

45 NMR (CDCl₃, δ) : 1.36 (3H, t, J=7Hz), 3.4 (3H, s), 3.6, 3.9 (each 2H, m), 3.90 (3H, s), 4.25 (2H, q, J=7Hz), 5.31 (2H, s), 5.98 (1H, d, J=15Hz), 6.6-7.8 (6H, m)

(7) Ethyl 5-[3,5-di-tert-butyl-4-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pentadienoate

IR (Neat) : 1710, 1625 cm⁻¹

Preparation 10

50 To a stirred solution of ethyl 5-[4-[(2-methoxyethoxy)methoxy]-3,5-dimethylphenyl]-(2E,4E)-2,4-pentadienoate (5.28 g) in methanol (55 ml) was added a solution of sodium hydroxide (6.32 g) in water (18 ml) below 20°C. After being stirred for an hour, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (200 ml) and adjusted to pH 4 with 10% hydrochloride solution. The resulting precipitate was collected by filtration and washed with water to give yellowish powder of 5-[4-[(2-methoxyethoxy)methoxy]-3,5-dimethylphenyl]-(2E,4E)-2,4-pentadienoic acid (4-13 g).

mp : 88-91°C

IR (Nujol): 2650, 1675, 1615, 1595, 1000, 970, 860 cm⁻¹

NMR (CDCl₃, δ) : 2.30 (6H, s), 3.43 (3H, s), 3.7, 4.0 (each 2H, m), 5.05 (2H, s), 5.95 (1H, d, J=15Hz), 6.75-7.8 (5H, m), 10.25 (1H, m)
 MASS (m/e) : 306 (M⁺), 89 (base)

5 Preparation 11

The following compounds were obtained according to a similar manner to that of Preparation 10.

- (1) 5-[3,5-Diisopropyl-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienoic acid
 mp : 96-113°C
 IR (Nujol) : 2600, 1685, 1615, 1595, 1100, 1080, 970 cm⁻¹
 NMR (CDCl₃, δ) : 1.25 (12H, d, J=8Hz), 3.45 (2H, sextet, J=8Hz), 3.43 (3H, s), 3.7, 4.0 (each 2H, m), 5.03 (2H, s), 6.0 (1H, d, J=15Hz), 6.8-7.8 (5H, m), 10.13 (1H, m)
 MASS (m/e) : 362 (M⁺), 89, 59 (base)
- (2) 5-[4-((2-Methoxyethoxy)methoxy)-3-methylphenyl]-(2E,4E)-2,4-pentadienoic acid
 mp : 117-119°C
 IR (Nujol) : 2600, 1670, 1600, 1000, 930 cm⁻¹
 NMR (CDCl₃, δ) : 2.26 (3H, s), 3.30 (3H, s), 3.6, 3.9 (each 2H, m), 5.32 (2H, s), 5.98 (1H, d, J=15Hz), 6.7-7.8 (6H, m), 8.7 (1H, m)
- (3) 5-[3-Chloro-4-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienoic acid
 mp : 130-135°C
 IR (Nujol) : 2600, 1680, 1615, 1590, 1050, 995 cm⁻¹
 NMR (CDCl₃, δ) : 3.30 (3H, s), 3.6, 3.9 (each 2H, m), 5.38 (2H, s), 6.01 (1H, d, J=15Hz), 6.7-7.7 (6H, m), 9.7 (1H, m)
- (4) 5-[3,5-Dichloro-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienoic acid
 mp : 116-120°C
 IR (Nujol) : 2600, 1690, 1630, 990, 905, 805 cm⁻¹
 NMR (CDCl₃, δ) : 3.40 (3H, s), 3.6, 4.1 (each 2H, m), 5.29 (2H, s), 6.05 (1H, d, J=15Hz), 6.7-7.7 (5H, m), 9.65 (1H, br)
 MASS (m/e) : 348 (M+2), 346 (M⁺), 89, 59 (base)
- (5) 5-[3-Methoxy-2-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienoic acid
 mp : 140-144°C
 IR (Nujol) : 2600, 1690, 1610, 1050, 955 cm⁻¹
 NMR (CDCl₃, δ) : 3.33 (3H, s), 3.5, 3.8 (each 2H, m), 3.80 (3H, s), 5.15 (2H, s), 5.93 (1H, d, J=15Hz), 6.7-7.7 (6H, m), 9.5 (1H, br)
- (6) 5-[4-Methoxy-3-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienoic acid
 mp : 121-125°C
 IR (Nujol) : 2600, 1670, 1620, 1590 cm⁻¹
 NMR (CDCl₃, δ) : 3.35 (3H, s), 3.55, 3.90 (each 2H, m), 3.86 (3H, s), 5.30 (2H, s), 5.92 (1H, d, J=15Hz), 6.7-7.7 (6H, m), 10.2 (1H, br)
- (7) 5-[3,5-Di-tert-butyl-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienoic acid
 IR (Nujol) : 2650, 1680, 1620, 970 cm⁻¹
 NMR (CDCl₃, δ) : 1.46 (18H, s), 3.42 (3H, s), 3.66, 3.96 (each 2H, m), 5.0 (2H, s), 5.97 (1H, d, J=15.5Hz), 6.6-7.7 (5H, m), 9.2 (1H, br)

45 Example 1

To a stirred mixture of 3-[3-methoxy-4-((2-methoxyethoxy)methoxy)phenyl]-(E)-propenoic acid (1.75 g) and triethylamine (1.81 ml) in dry N,N-dimethylformamide (10 ml) was added slowly diphenyl phosphinic chloride (1.47 g) at -10 to -15°C under an inert atmosphere. After being stirred for 30 minutes, a solution of 1-(2-aminoethyl)-4-(3-indolyl)piperidine (1.5 g) in dry N,N-dimethylformamide (10 ml) was added slowly to the reaction mixture at -10°C. After being stirred for 1 hour at ambient temperature, the reaction mixture was poured into ice-water (200 ml) and extracted with chloroform (100 ml). The extract was washed with a saturated sodium chloride solution and dried over magnesium sulfate. The solvent was distilled off and the residue was subjected to column chromatography on silica gel (47 g) and eluted with a mixture of chloroform and methanol (10:1). The fractions containing the object compound were combined and concentrated under reduced pressure to give syrup of 1-[2-[3-[3-methoxy-4-((2-methoxyethoxy)methoxy)phenyl]-(E)-propenoylamino]ethyl]-4-(3-indolyl)piperidine (2.8 g).

NMR (CDCl₃, δ) : 1.6-3.3 (11H, m), 3.37 (3H, s), 3.55 (4H, m), 3.85 (2H, m), 3.89 (3H, s), 5.32 (2H, s),

6.35 (1H, d, J=15.0Hz), 6.52 (1H, br s), 6.9-7.8 (8H, m), 7.57 (1H, d, J=15.0Hz), 8.25 (1H, br s)

Example 2

- 5 The following compounds were obtained according to a similar manner to that of Example 1.
- (1) 1-[2-[5-[3-Methoxy-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienylamino]ethyl]-4-(3-indolyl)piperidine
 IR (Nujol) : 3300, 1660, 1260, 1092, 990, 744 cm^{-1}
 NMR (CDCl_3 , δ) : 1.6-3.3 (11H, m), 3.35 (3H, s), 3.54 (4H, m), 3.84 (2H, m), 3.86 (3H, s), 5.30 (2H, s), 6.07 (1H, d, 15.0Hz), 6.70-7.80 (12H, m), 9.30 (1H, s)
 10 MASS : 533 (M^+), 213
- (2) 1-[3-[5-[3-Methoxy-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienylamino]propyl]-4-(3-indolyl)piperidine
 NMR (CDCl_3 , δ) : 1.5-3.6 (15H, m), 3.36 (3H, s), 3.6 (2H, m), 3.87 (3H, s), 3.90 (2H, m), 5.35 (2H, s), 6.02 (1H, d, J=14.4Hz), 6.6-7.9 (12H, m), 8.55 (1H, s)
 15 MASS : 547 (M^+)
- (3) 1-[4-[5-[3-Methoxy-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienylamino]butyl]-4-(3-indolyl)piperidine
 IR (Nujol) : 3400, 3200 (broad), 1650, 1377, 1260 cm^{-1}
 20 NMR (CDCl_3 , δ) : 1.3-3.4 (17H, m), 3.33 (3H, s), 3.55 (2H, m), 3.80 (5H, br s), 5.27 (2H, s), 6.11 (1H, d, J=15.0Hz), 6.5-8.0 (12H, m), 9.23 (1H, s)
 MASS : 561 (M^+)
- (4) 1-[2-[5-(3,4-Dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino]ethyl]-4-(3-indolyl)piperidine
 mp : 196-198°C (recrystallized from ethanol)
 25 IR (Nujol) : 3280, 1640, 1610, 1590, 1550, 1510 cm^{-1}
 NMR ($\text{DMSO}-d_6$, δ) : 1.4-3.5 (13H, m), 3.78 (3H, s), 3.81 (3H, s), 6.15 (1H, d, J=15.0Hz), 6.8-7.6 (11H, m), 7.99 (1H, br t), 10.75 (1H, br s)
 MASS : 459 (M^+), 213
- Elemental Analysis : $\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_3$
 30 Calcd. : C 73.18, H 7.24, N 9.14
 Found : C 73.84, H 7.42, N 8.72
- (5) 1-[2-[5-(3,4,5-Trimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino]ethyl]-4-(3-indolyl)piperidine
 mp : 86-100°C
 IR (Nujol) : 3250, 1650, 1610, 1580 cm^{-1}
 35 NMR ($\text{DMSO}-d_6$, δ) : 1.4-3.6 (13H, m), 3.70 (3H, s), 3.83 (6H, s), 6.19 (1H, d, J=15.0Hz), 6.7-7.7 (10H, m), 8.02 (1H, br t), 10.74 (1H, br s)
 MASS : 489 (M^+) 289, 213
- Elemental Analysis : $\text{C}_{29}\text{H}_{35}\text{N}_3\text{O}_4 \cdot 3/4\text{H}_2\text{O}$
 40 Calcd. : C 69.23, H 7.31, N 8.35
 Found : C 69.38, H 7.08, N 8.40
- (6) 1-[2-[3-(4-Hydroxy-3-methoxyphenyl)-(E)-propenyl-amino]ethyl]-4-(3-indolyl)piperidine
 mp : 115-135°C
 IR (Nujol) : 3300 (broad), 1655, 1588, 1512 cm^{-1}
- (7) 1-[2-[5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienylamino]ethyl]-4-(3-indolyl)piperidine
 45 mp : 115-131°C
 IR (Nujol) : 3330 (broad), 1660, 1377 cm^{-1}
- (8) 1-[3-[5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienylamino]propyl]-4-(3-indolyl)piperidine
 mp : 150-170°C
 IR (Nujol) : 3400, 3200 (broad), 1638, 1580 cm^{-1}
- (9) 1-[4-[5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienylamino]butyl]-4-(3-indolyl)piperidine
 50 mp : 150-170°C
 IR (Nujol) : 3200 (broad), 1640, 1580, 1270, 735 cm^{-1}
- (10) 1-[2-[5-[3,4-Bis((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienylamino]ethyl]-4-(3-indolyl)-piperidine
- 55 This compounds was used as a starting compound of Example 7-(4) without purification.
- (11) 1-[2-[5-[3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienylamino]ethyl]-4-(3-indolyl)piperidine
 IR (Nujol) : 3300, 1650, 1610, 1580, 1125, 990, 960, 845, 745 cm^{-1}

- (12) 1-[3-[5-[3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienoylamino]propyl]-4-(3-indolyl)piperidine
IR (Neat) : 3300, 3000, 2990, 1650, 1615, 1580, 1130, 990, 960, 850 cm^{-1}
- (13) 1-[4-[5-[3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienoylamino]butyl]-4-(3-indolyl)piperidine
IR (Neat) : 2900, 1650, 1610, 1580, 1550, 1120, 960, 850, 740 cm^{-1}
- (14) 1-[2-[5-[4-((2-Methoxyethoxy)methoxy)-3,5-dimethylphenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
mp : 163-164°C (recrystallized from ethyl acetate)
IR (Nujol) : 3450, 3300, 1645, 1615, 990, 970 cm^{-1}
NMR (DMSO- d_6 , δ) : 1.5-2.3 (6H, m), 2.34 (6H, s), 2.5-3.1 (7H, m), 3.25 (3H, s), 3.5, 3.8 (each 2H, m), 5.05 (2H, s), 6.15 (1H, d, $J=15\text{Hz}$), 6.8-7.7 (10H, m), 8.03 (1H, m), 10.7 (1H, m)
MASS (m/e) : 531 (M^+), 213 (base)
- (15) 1-[2-[5-[3,5-Diisopropyl-4-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
IR (Neat) : 1660, 1650, 1615, 970 cm^{-1}
- (16) 1-[2-[5-[4-((2-Methoxyethoxy)methoxy)-3-methyl-phenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
mp : 140-144°C
IR (Nujol) : 3470, 3280, 1640, 1610, 1595, 1000, 980 cm^{-1}
NMR (CDCl_3 , δ) : 1.6-3.2 (13H, m), 2.25 (3H, s), 3.38 (3H, s), 3.6, 3.8 (each, 2H, m), 5.32 (2H, s), 5.96 (1H, d, $J=15\text{Hz}$), 6.2-7.8 (11H, m), 8.25 (1H, m)
MASS (m/e) : 517 (M^+), 213 (base)
- (17) 1-[2-[5-[3-Chloro-4-((2-methoxyethoxy)methoxy)-phenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3450, 3300, 1645, 1610, 1050, 990 cm^{-1}
NMR (DMSO- d_6 , δ) : 1.5-2.5 (6H, m), 2.8-3.2 (7H, m), 3.65 (3H, s), 3.6, 3.8 (each 2H, m), 5.39 (2H, s), 6.10 (1H, d, $J=15\text{Hz}$), 6.8-7.9 (11H, m), 8.05 (1H, m), 10.7S (1H, m)
MASS (m/e) : 537, 213 (base)
- (18) 1-[2-[5-[3,4-Dihydroxyphenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3400, 3350, 1650, 1585, 1520 cm^{-1}
MASS (m/e) : 431 (M^+), 213 (base)
- (19) 1-[2-[5-[4-Hydroxy-3,5-dimethoxyphenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3420, 1665, 1650, 1620, 1590, 1530, 1515, 1120 cm^{-1}
MASS (m/e) : 475 (M^+), 213
- (20) 1-[4-[5-[4-Hydroxy-3,5-dimethoxyphenyl]-(2E,4E)-2,4-pentadienoylamino]butyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3250, 1640, 1600, 1540, 1510, 1130, 1110, 810 cm^{-1}
- (21) 1-[3-[5-[4-Hydroxy-3,5-dimethoxyphenyl]-(2E,4E)-2,4-pentadienoylamino]propyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3420, 1658, 1610, 1575, 1550, 1510, 1120 cm^{-1}
MASS (m/e) : 489 (M^+), 239, 233, 213 (base), 197
- (22) 1-[2-[5-[4-Acetoxy-3-methoxyphenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3440, 3250, 1760, 1655, 1620, 1560, 1505 cm^{-1}
MASS (m/e) : 487 (M^+), 213 (base)
- (23) 1-[2-[5-[3-Methoxy-4-propionyloxyphenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3430, 3250, 3060, 1750, 1655, 1620, 1560 cm^{-1}
MASS (m/e) : 501 (M^+), 213 (base)
- (24) 1-[2-[5-[4-Ethoxycarbonyloxy-3,5-dimethoxyphenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3360, 3300, 1750, 1640, 1590, 1130, 1000, 735 cm^{-1}
MASS (m/e) : 547 (M^+), 228, 213 (base)
- (25) 1-[4-[5-[4-Ethoxycarbonyloxy-3,5-dimethoxyphenyl]-(2E,4E)-2,4-pentadienoylamino]butyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3380, 3250, 1750, 1655, 1620, 1595, 1555, 1130, 1050, 1000, 735 cm^{-1}
MASS (m/e) : 575 (M^+), 531, 503, 285, 233, 213 (base)

- (26) 1-[2-{5-(4-Hydroxy-3,5-dimethylphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)-piperidine
IR (Nujol) : 3300, 1640, 1590, 1545, 990, 860 cm^{-1}
MASS (m/e) : 443 (M^+), 213 (base)
- 5 (27) 1-[2-{5-(4-Hydroxy-3,5-diisopropylphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)-piperidine
IR (Nujol) : 3400, 3300, 1650, 1630, 1585, 995, 870 cm^{-1}
MASS (m/e) : 499 (M^+), 226, 213 (base)
- 10 (28) 1-[2-{5-(4-Hydroxy-3-methylphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3200, 1640, 1575, 1550, 1000 cm^{-1}
MASS (m/e) : 429 (M^+), 213 (base)
- (29) 1-[2-{5-(3-Chloro-4-hydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3420, 1650, 1590, 1000 cm^{-1}
MASS (m/e) : 449 (M^+), 213 (base)
- 15 (30) 1-[2-{5-(4-Acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3380, 3320, 1755, 1650, 1620, 1595, 990, 745 cm^{-1}
MASS (m/e) : 517 (M^+), 213 (base)
- 20 (31) 1-[2-{5-[3,5-Dichloro-4-[(2-methoxyethoxy)methoxy]-phenyl]-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Neat) : 1655, 1610, 995 cm^{-1}
- (32) 1-[2-{5-[3-Methoxy-2-[(2-methoxyethoxy)methoxy]-phenyl]-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Neat) : 1650, 1610, 1000, 960 cm^{-1}
- 25 (33) 1-[2-{5-[4-Methoxy-3-[(2-methoxyethoxy)methoxy]-phenyl]-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
mp : 135-136°C (recrystallized from ethyl acetate)
IR (Nujol) : 3260, 1640, 1615, 1595, 1550, 1510 cm^{-1}
NMR (DMSO-d_6 , δ) : 3.75 (3H, s), 5.23 (2H, s), 6.11 (1H, d, $J=15\text{Hz}$), 6.7-7.6 (11H, m), 7.96 (1H, t like), 10.7 (1H, br)
MASS (m/e) : 533, 445, 333, 213 (base)
- 30 (34) 1-[2-{5-[3,5-Di-tert-butyl-4-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
mp : 98-103°C (recrystallized from ethanol)
IR (Nujol) : 3300, 1650, 1600, 970 cm^{-1}
NMR (CDCl_3 , δ) : 1.42 (18H, s), 1.6-2.3 (6H, m), 2.53 (2H, t, $J=7\text{Hz}$), 2.8 (3H, m), 3.35 (3H, s), 3.5 (2H, m), 3.66, 3.96 (each 2H, m), 4.93 (2H, s), 5.95 (1H, d, $J=15.5\text{Hz}$), 6.17 (1H, t like), 6.6-7.7 (10H, m), 8.2 (1H, s)
- 35 (35) 1-[2-{5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3550, 3300, 3230, 1650, 1610, 1590, 1000 cm^{-1}
MASS (m/e) : 527 (M^+), 226, 213
- (36) 1-[2-{5-(3,5-Dichloro-4-hydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)-piperidine
MASS (m/e) : 485 ($\text{M}+2$), 483 (M^+), 213 (base)
- 40 (37) 1-[2-{5-(2-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3400, 3240, 1650, 1605, 1600, 1530, 1090, 1005 cm^{-1}
MASS (m/e) : 4:5 (M^+), 226, 213 (base)
- (38) 1-[2-{5-(3-Hydroxy-4-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3350, 1650, 1615, 1590 cm^{-1}
MASS (m/e) : 445 (M^+), 213 (base)
- 50 (39) 1-[2-{5-[3,4-bis(Ethoxycarbonyloxy)phenyl]-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
IR (Nujol) : 3500, 3350, 1775, 1650, 1620, 1000 cm^{-1}
MASS (m/e) : 529 (M^+-46), 457, 285 (base), 213
- 55

Example 3

To a solution of 1-[2-{5-[3,5-di-tert-butyl-4-[(2-methoxyethoxy)methoxy]phenyl]-(2E,4E)-2,4-pen-

tadienoylamino]ethyl]-4-(3-indolyl)piperidine (0.5 g) in methanol (5 ml) was added dropwise methanesulfonic acid (0.26 ml) at 18-25°C. After 2 hours the reaction mixture was adjusted to pH 7.5 with 2N-sodium hydroxide and then poured into saturated sodium bicarbonate solution (50 ml). The resulting precipitate was collected and washed with water. The precipitate was subjected to column chromatography on silica gel and eluted with a mixture of chloroform and methanol (20:1, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure. The residue was recrystallized from 1,4-dioxane, to give white crystals of 1-[2-[5-(3,5-di-tert-butyl-4-hydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine (0.28 g). See Example 2-(35).

mp : 108-115°C
 IR (Nujol) : 3550, 3300, 3230, 1650, 1610, 1590, 1000 cm⁻¹
 NMR (CDCl₃, δ) : 1.43 (18H, s), 1.6-2.3 (6H, m), 2.53 (2H, t, J=7Hz), 2.7-3.2 (3H, m), 3.45 (2H, m), 5.33 (1H, s), 5.93 (1H, d, J=15.5Hz), 6.15 (1H, t like), 6.65-7.7 (10H, m), 8.16 (1H, s)
 MASS (m/e) : 527 (M⁺), 226, 213

15 Example 4

To a stirred solution of 1-[2-[5-[3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)piperidine (10.0 g) in methanol (100 ml) was added slowly methanesulfonic acid (2.3 ml) at ambient temperature. After stirring for 2 hours, the reaction mixture was adjusted to pH 7.2 with aqueous 2N sodium hydroxide solution, and poured into a solution of 4.5 g of sodium bicarbonate in 500 ml of water. After stirring for 30 minutes, the resulting precipitate was collected by filtration and washed with 100 ml of water. The residue was subjected to column chromatography on silica gel and eluted with a mixture of chloroform and methanol. The fractions containing the object compound were combined and concentrated under reduced pressure. The residue was recrystallized from ethanol to give 1-[2-[5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino]ethyl]-4-(3-indolyl)-piperidine (6.69 g). See Example 2-(19).

mp : 199-202°C (dec.)
 IR (Nujol) : 3420, 1665, 1650, 1620, 1590, 1530, 1515, 1120 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.5-2.4 (7H, m), 2.7-3.5 (6H, m), 3.81 (6H, s), 6.15 (1H, d, J=14Hz), 6.8-7.8 (10H, m), 8.0 (1H, t like), 8.68 (1H, m), 10.75 (1H, s)
 MASS (m/e) : 475 (M⁺), 213
 Elemental Analysis : C₂₈H₃₃N₃O₄
 Calcd. : C 70.71, H 6.99, N 8.83
 Found : C 70.34, H 6.56, N 8.65

35 Example 5

A mixture of 1-[3-[5-[3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienoylamino]-propyl]-4-(3-indolyl)piperidine (1.67 g) and p-toluene-sulfonic acid monohydrate (0.64 g) in methanol (33 ml) was refluxed for 30 minutes under an inert atmosphere. Upon cooling to ambient temperature, the mixture was added dropwise to an aqueous sodium carbonate solution. The resulting powder was subjected to column chromatography on silica gel and eluted with a mixture of chloroform and methanol (10:1, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure. The obtained residue was recrystallized from a mixture of ethanol and water (7:3, V/V) to give 1-[3-[5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino]propyl]-4-(3-indolyl)piperidine (0.51 g). See Example 2-(21).

mp : 176-179°C (recrystallized from ethanol-water (8:2, v/v))
 IR (Nujol) : 3420, 1658, 1610, 1575, 1550, 1510, 1120 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.4-2.5 (9H, m), 2.6-3.5 (6H, m), 3.79 (6H, s), 6.10 (1H, d, J=15Hz), 6.7-7.7 (10H, m), 8.05 (1H, t like), 8.7 (1H, m), 10.72 (1H, s)
 MASS (m/e) : 489 (M⁺), 239, 233, 213 (base), 197
 Elemental Analysis : C₂₉H₃₅N₃O₄
 Calcd. : C 71.14, H 7.20, N 8.58
 Found : C 70.79, H 7.12, N 8.57

55 Example 6

A mixture of 1-[2-[3-[3-methoxy-4-((2-methoxyethoxy)-methoxy)phenyl]-(E)-propenoylamino]ethyl]-4-(3-indolyl)-piperidine (2 g) and p-toluenesulfonic acid monohydrate (1.05 g) in methanol (40 ml) was refluxed for

30 minutes under an inert atmosphere. After the solvent was removed under reduced pressure, the residue was treated with water (100 ml), adjusted to pH 10.0 with a sodium carbonate solution and extracted with ethyl acetate. The extract was washed with a saturated sodium chloride solution and dried over magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (31 g) and eluted with a mixture of chloroform and methanol (8:1, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure to give 1-[2-{3-(4-hydroxy-3-methoxyphenyl)-(E)-propenoylamino}-ethyl]-4-(3-indolyl)piperidine (0.89 g). See Example 2-(6).

mp : 115-135°C

IR (Nujol) : 3300 (broad), 1655, 1588, 1512 cm⁻¹

NMR (DMSO-d₆, δ) : 1.5-3.6 (14H, m), 3.83 (3H, s), 6.50 (1H, d, J=15.0Hz), 6.7-7.7 (9H, m), 7.83 (1H, br t), 10.70 (1H, s)

MASS : 419 (M⁺), 213

Elemental Analysis : C₂₆H₂₉N₃O₃·1/2H₂O

Calcd. : C 70.00, H 7.06, N 9.80

Found : C 70.18, H 6.92, N 9.85

Example 7

The following compounds were obtained according to similar manners to those of Examples 3 to 6.

(1) 1-[2-{5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
See Example 2-(7).

mp : 115-131°C

IR (Nujol) : 3330 (broad), 1660, 1377 cm⁻¹

NMR (DMSO-d₆, δ) : 1.5-3.6 (13H, m), 3.82 (3H, s), 6.07 (1H, d, J=15.0Hz), 6.6-7.6 (8H, m), 7.90 (1H, br t), 9.20 (1H, s), 10.68 (1H, s)

MASS : 445 (M⁺), 213

Elemental Analysis : C₂₇H₃₁N₃O₃·1/2H₂O

Calcd. : C 71.34, H 7.10, N 9.24

Found : C 71.15, H 6.87, N 9.19

(2) 1-[3-{5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}propyl]-4-(3-indolyl)piperidine
See Example 2-(8).

mp : 150-170°C

IR (Nujol) : 3400, 3200 (broad), 1638, 1580 cm⁻¹

NMR (DMSO-d₆, δ) : 1.5-3.8 (15H, m), 3.86 (3H, s), 4.20 (1H, broad), 6.15 (1H, d, J=14.0Hz), 6.6-7.8 (11H, m), 8.26 (1H, br s), 10.82 (1H, s)

MASS : 459 (M⁺), 213

Elemental Analysis : C₂₈H₃₃N₃O₃·1/2CHCl₃·1/2C₂H₅OC₂H₅

Calcd. : C 65.85, H 6.97, N 7.55

Found : C 65.67, H 7.18, N 7.87

(3) 1-[4-{5-(4-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}butyl]-4-(3-indolyl)piperidine
See Example 2-(9).

mp : 150-170°C

IR (Nujol) : 3200 (broad), 1640, 1580, 1270, 735 cm⁻¹

NMR (DMSO-d₆, δ) : 1.2-3.7 (17H, m), 3.80 (3H, s), 6.07 (1H, d, J=15.0Hz), 6.6-7.8 (11H, m), 8.10 (1H, s), 9.25 (1H, s), 10.82 (1H, s)

MASS : 473 (M⁺), 213

Elemental Analysis : C₂₉H₃₅N₃O₃·1/2CHCl₃·1/2C₂H₅OC₂H₅

Calcd. : C 66.33, H 7.16, N 7.37

Found : C 66.02, H 7.47, N 7.33

(4) 1-[2-{5-(3,4-Dihydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine
See Example 2-(18).

mp : 138-158°C (dec.) (recrystallized from ethanol-water (8:2, V/V))

IR (Nujol) : 3400, 3350, 1650, 1585, 1520 cm⁻¹

NMR (DMSO-d₆, δ) : 1.5-3.6 (13H, m), 6.13 (1H, d, J=15Hz), 6.63-7.70 (11H, m), 7.93 (1H, m), 10.73 (1H, br)

MASS (m/e) : 431 (M⁺), 213 (base)

Elemental Analysis : C₂₆H₂₉N₃O₃·6/5 ethanol

Calcd. : C 70.07, H 7.49, N 8.63

Found : C 69.77, H 7.39, N 8.67

(5) 1-[4-{5-(4-Hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}butyl]-4-(3-indolyl)piperidine See Example 2-(20).

IR (Nujol) : 3250, 1640, 1600, 1540, 1510, 1130, 1110, 810 cm^{-1}

5 (6) 1-[2-{5-(4-Hydroxy-3,5-dimethylphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine See Example 2-(26).

mp : 125-135°C (recrystallized from ethanol-water (8:2, v/v))

IR (Nujol) : 3300, 1640, 1590, 1545, 990, 860 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 1.4-2.4 (6H, m), 2.19 (6H, s), 2.6-3.2 (7H, m), 6.11 (1H, d, J=15Hz), 6.7-7.6 (10H, m), 7.95 (1H, m), 10.82 (1H, m)

MASS (m/e) : 443 (M^+), 213 (base)

Elemental Analysis : $\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_2 \cdot 4/3\text{H}_2\text{O}$

Calcd. : C 71.92, H 7.69, N 8.99

Found : C 72.00, H 7.69, N 8.88

15 (7) 1-[2-{5-(4-Hydroxy-3,5-diisopropylphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine See Example 2-(27).

mp : 110-120°C (recrystallized from ethanol-water (8:2, v/v))

IR (Nujol) : 3400, 3300, 1650, 1630, 1585, 995 870 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 1.28 (12H, d, J=8Hz), 1.5-2.4 (6H, m), 2.7-3.6 (9H, m), 6.13 (1H, d, J=15Hz), 6.8-7.6 (10H, m), 7.95 (1H, m), 8.4 (1H, m), 10.73 (1H, m)

MASS (m/e) : 499 (M^+), 226, 213 (base)

Elemental Analysis : $\text{C}_{32}\text{H}_{41}\text{N}_3\text{O}_2 \cdot \text{H}_2\text{O}$

Calcd. : C 74.24, H 8.37, N 8.11

Found : C 73.84, H 8.42, N 7.97

25 (8) 1-[2-{5-(4-Hydroxy-3-methylphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine See Example 2-(28).

mp : 138-141°C (recrystallized from a mixture of ethanol-water (8:2, v/v))

I.R (Nujol) : 3200, 1640, 1575, 1550, 1000 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 1.5-3.6 (13H, m), 2.20 (3H, s), 6.10 (1H, d, J=15Hz), 6.7-7.7 (11H, m), 7.93 (1H, m), 9.65 (1H, m), 10.73 (1H, m)

MASS (m/e) : 429 (M^+), 213 (base)

Elemental Analysis : $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_2 \cdot 5/4\text{H}_2\text{O}$

Calcd. : C 71.73, H 7.47, N 9.29

Found : C 71.78, H 7.73, N 9.28

35 (9) 1-[2-{5-(3-Chloro-4-hydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine See Example 2-(29).

mp : 139-155°C (recrystallized from ethanol-water)

IR (Nujol) : 3420, 1650, 1590, 1000 cm^{-1}

40 NMR (DMSO- d_6 , δ) : 1.5-3.5 (13H, m), 6.12 (1H, d, J=15Hz), 6-7-7-7 (11H, m), 7.98 (1H, m), 10.7 (1H, m)

MASS (m/e) : 449 (M^+), 213 (base)

Elemental Analysis : $\text{C}_{26}\text{H}_{28}\text{ClN}_3\text{O}_2 \cdot 1.5\text{H}_2\text{O}$

Calcd. : C 65.47, H 6.55, N 8.81

Found : C 65.88, H 6.44, N 8.78

45 (10) 1-[2-{5-(3,5-Dichloro-4-hydroxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine See Example 2-(36).

mp : 165-175°C (recrystallized from N,N-dimethylformamide)

50 NMR (DMSO- d_6 , δ) : 1.5-3.6 (13H, m), 5.3 (1H, m), 6.08 (1H, d, J=15Hz), 6.6-7.6 (10H, m), 8.09 (1H, m), 10.75 (1H, s)

MASS (m/e) : 485 ($M+2$), 483 (M^+), 213 (base)

(11) 1-[2-{5-(2-Hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine See Example 2-(37).

mp : 184-186°C (recrystallized from ethanol)

IR (Nujol) : 3400, 3240, 1650, 1605, 1600, 1530, 1090, 1005 cm^{-1}

55 NMR (DMSO- d_6 , δ) : 1.4-3.6 (13H, m), 3.78 (3H, s), 6.11 (1H, d, J=15Hz), 6.6-7.65 (11H, m), 7.90 (1H, t like), 8.95 (1H, br), 10.75 (1H, s)

MASS (m/e) : 445 (M^+), 226, 213 (base)

(12) 1-[2-{5-(3-Hydroxy-4-methoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine

See Example 2-(38).

mp : 135-140°C (recrystallized from ethanol)

IR (Nujol) : 3350, 1650, 1615, 1590 cm⁻¹

NMR (DMSO-d₆, δ) : 1.4-3.5 (13H, m), 3.75 (3H, s), 6.11 (1H, d, J=15Hz), 6.6-7.7 (11H, m), 7.91 (1H, t like), 9.0 (1H, br), 10.7 (1H, s)

MASS (m/e) : 445 (M⁺), 213 (base)

Example 8

To a mixture of 1-[2-{5-(4-hydroxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)-piperidine (0.89 g), dry N-methylmorpholine (1.0 g) and dry N,N-dimethylformamide (10 ml) was added slowly acetyl chloride (0.26 g) at 5 to 10°C. After stirring for 1 hour, the reaction mixture was poured into water (50 ml) and stirred for 1 hour. The resulting precipitate was collected, washed with water and then recrystallized from a mixture of ethanol and water (7:3, V/V) to give 1-[2-{5-(4-acetoxy-3-methoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine (0.22 g). See Example 2-(22).

mp : 101-105°C (recrystallized from ethanol-water (8:2, v/v))

IR (Nujol) : 3440, 3250, 1760, 1655, 1620, 1560, 1505 cm⁻¹

NMR (DMSO-d₆, δ) : 1.5-2.4 (6H, m), 2.24 (3H, s), 2.6-3.5 (7H, m), 3.81 (3H, s), 6.20 (1H, d, J=15Hz), 6.8-7.7 (11H, m), 8.04 (1H, m), 10.73 (1H, s)

MASS (m/e) : 487 (M⁺), 213 (base)

Elemental Analysis : C₂₉H₃₃N₃O₄·H₂O

Calcd. : C 68.89, H 6.98, N 8.31

Found : C 68.91, H 6.95, N 8.32

Example 9

1-[2-{5-(3-Methoxy-4-propionyloxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine was obtained according to a similar manner to that of Example 8. See Example 2-(23).

mp : 157-158°C (recrystallized from ethanol)

IR (Nujol) : 3430, 3250, 3060, 1750, 1655, 1620, 1560 cm⁻¹

NMR (DMSO-d₆, δ) : 1.15 (3H, t, J=8Hz), 1.5-2.4 (6H, m), 2.62 (2H, q, J=8Hz), 2.4-3.2 (5H, m), 3.33 (2H, m), 3.82 (3H, s), 6.22 (1H, d, J=15Hz), 6.8-7.7 (11H, m), 8.05 (1H, m), 10.75 (1H, s)

MASS (m/e) : 501 (M⁺), 213 (base)

Elemental Analysis : C₃₀H₃₅N₃O₄·H₂O

Calcd. : C 69.34, H 7.18, N 8.09

Found : C 69.14, H 7.09, N 8.06

Example 10

To a mixture of 1-[2-{5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine (1 g) and pyridine (10 ml) was added slowly acetyl chloride (0.48 ml) at 5 to 10°C. After 1 hour, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. The solvent was distilled off and the residue was subjected to column chromatography on silica gel and eluted with a mixture of chloroform and methanol (10:1, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure. The residue was treated with a mixture of fumaric acid (83 mg) and methanol (8 ml) and concentrated under reduced pressure to give white crystals. The crystals were recrystallized from ethanol to give 1-[2-{5-(4-acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine 1/2 fumarate (0.15 g).

mp : 202-209°C

IR (Nujol) : 3400, 1750, 1680, 1615, 1595, 1565 cm⁻¹

NMR (DMSO-d₆, δ) : 1.6-2.15 (5H, m), 2.32 (3H, s), 2.2-3.6 (8H, m), 4.82 (6H, s), 6.22 (1H, d, J=14Hz), 6-6.4 (1H, s), 6.7-7.7 (10H, m), 8.29 (1H, m), 10.75 (1H, s)

MASS (m/e) : 517 (M⁺), 213 (base)

Elemental Analysis : C₃₀H₃₅N₃O₅·1/2Fumarate·3/2H₂O

Calcd. : C 63.77, H 6.68, N 6.97

Found : C 63.57, H 6.44, N 6.95

Example 11

1-[2-{5-(3,5-Dimethoxy-4-propionyloxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine 1/2fumarate was obtained according to a similar manner to that of Example 10.

5 mp : 188-192°C (recrystallized from ethanol)

IR (Nujol) : 3400, 1745, 1680, 1615, 1595, 1565 cm⁻¹

NMR (DMSO-d₆, δ) : 1.13 (3H, t, J=7Hz), 1.6-2.2 (3H, m), 2.2-3.7 (12H, m), 3.81 (6H, s), 6.21 (1H, d, J=15Hz), 6.62 (1H, s), 6.8-7.6 (10H, m), 8.3 (1H, m), 10.78 (1H, s)

MASS (m/e) : 531 (M⁺), 213 (base)

10 Elemental Analysis : C₃₁H₃₇N₃O₅·1/2Fumarate·3/2H₂O

Calcd. : C 64.27, H 6.86, N 6.81

Found : C 64.17, H 6.78, N 6.78

Example 12

15

To a mixture of 1-[2-{5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine (1.19 g), triethylamine (1.74 ml) and dry N,N-dimethylformamide (12 ml) was added slowly a mixture of ethyl chloroformate (0.33 g) and methylene chloride (0.5 ml) at 0 to 5°C. Similar work up gave 1-[2-{5-(4-ethoxycarbonyloxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine (0.74 g). See Example 2-(24).

mp : 90-98°C (recrystallized from ethanol-water (8:2, V/V))

IR (Nujol) : 3360, 3300, 1750, 1640, 1590, 1130, 1000, 735 cm⁻¹

NMR (DMSO-d₆, δ) : 1.28 (3H, t, J=8Hz), 1.5-3.6 (13H, m), 3.81 (6H, s), 4.23 (2H, q, J=8Hz), 6.21 (1H, d, J=15Hz), 6.8-7.7 (10H, m), 8.05 (1H, m), 10.71 (1H, s)

25 MASS (m/e) : 547 (M⁺), 228, 213 (base)

Elemental Analysis : C₃₁H₃₇N₃O₆·2.5H₂O

Calcd. : C 62.82, H 7.14, N 7.09

Found : C 62.74, H 6.93, N 7.05

Example 13

30

The following compounds were obtained according to a similar manner to that of Example 12.

(1) 1-[4-{5-(4-Ethoxycarbonyloxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}butyl]-4-(3-indolyl)piperidine See Example 2-(25).

35 mp : 90-98°C (recrystallized from ethanol-water (8:2, v/v))

IR (Nujol) : 3380, 3250, 1750, 1655, 1620, 1595, 1555, 1130, 1050, 1000, 735 cm⁻¹

NMR (DMSO-d₆, δ) : 1.27 (3H, t, J=8Hz), 1.4-3.7 (17H, m), 3.72 (6H, s), 4.23 (2H, q, J=8Hz), 6.20 (1H, d, J=15Hz), 6.8-7.75 (10H, m), 8.10 (1H, m), 10.76 (1H, s)

MASS (m/e) : 575 (M⁺), 531, 503, 285, 233, 213 (base)

40 Elemental Analysis : C₃₃H₄₁N₃O₆·3/2ethanol

Calcd. : C 37.01, H 7.81, N 6.52

Found : C 66.39, H 7.74, N 6.52

(2) 1-[4-{5-(3,5-Dimethoxy-4-propionyloxyphenyl)-(2E,4E)-2,4-pentadienoylamino}butyl]-4-(3-indolyl)piperidine hydrochloride

45 mp : 215-220°C (recrystallized from acetonitrile)

IR (Nujol) : 3250, 2650, 2500, 1760, 1650, 1595, 1130, 1010, 850, 750 cm⁻¹

NMR (CDCl₃, δ) : 1.29 (3H, t, J=8Hz), 2.65 (2H, q, J=8Hz), 1.5-3.7 (17H, m), 3.80 (6H, s), 6.35 (1H, d, J=15Hz), 6.6-7.7 (10H, m), 7.9 (1H, m), 9.05 (1H, m), 11.3 (1H, m)

MASS (m/e) : 559 (M⁺), 503, 233, 213 (base)

50 (3) 1-[2-{5-[3,4-bis(Ethoxycarbonyloxy)phenyl]-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine See Example 2-(39).

mp : 135-137°C (recrystallized from a mixture of water and ethanol)

IR (Nujol) : 3500, 3350, 1775, 1650, 1620, 1000 cm⁻¹

55 NMR (DMSO-d₆, δ) : 1.30 (6H, t, J=8Hz), 1.3-3.5 (13H, m), 4.30 (4H, q, J=8Hz), 6.25 (1H, d, J=15Hz), 6.6-7.7 (11H, m), 8.08 (1H, m), 10.73 (1H, s)

MASS (m/e) : 529 (M⁺-46), 457, 285 (base), 213

Example 14

To a mixture of 1-[2-{5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine (2.0 g), triethylamine (2.9 ml) and dry N,N-dimethylformamide (20 ml) was added slowly a solution of acetylchloride (0.5 g) in methylene chloride (1.0 ml) at 0 to 5°C. After 1 hour, the reaction mixture was poured into water (200 ml) and stirred for 1 hour. The resulting precipitate was collected, washed with water and air-dried at ambient temperature. The precipitate was subjected to column chromatography on silica gel (60 g) and eluted with a mixture of chloroform and methanol (20:1, V/V). The fractions containing the object compound were combined and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give pale yellow crystals of 1-[2-{5-(4-acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine (1.35 g). See Example 2-(30).

mp : 169-172°C

IR (Nujol) : 3380, 3320, 1755, 1650, 1620, 1595, 990, 745 cm⁻¹

NMR (CDCl₃, δ) : 1.5-3.6 (13H, m), 2.32 (3H, s), 3.82 (6H, s), 6.0 (1H, d, J=15Hz), 6.34 (1H, m), 6.7-7.7 (10H, m), 8.32 (1H, m)

MASS (m/e) : 517 (M⁺), 213 (base)

Elemental Analysis : C₃₀H₃₅N₃O₅

Calcd. : C 69.61, H 6.82, N 8.12

Found : C 69.35, H 6.82, N 8.02

Example 15

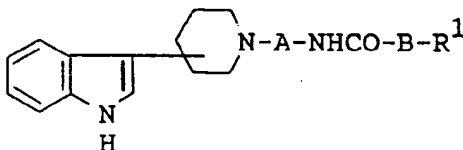
To a stirred mixture of 5-[3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienoic acid (1.35 g) and triethylamine (1.17 ml) in dry N,N-dimethylformamide (8 ml) was added slowly diphenyl phosphinic chloride (0.97 g) at -10 to -15°C under an inert atmosphere. After being stirred for 1 hour, a solution of 1-(2-aminoethyl)-4-(3-indolyl)piperidine (0.97 g) in dry N,N-dimethylformamide (8 ml) was added slowly to the reaction mixture at the same temperature. After being stirred for 40 minutes at the same temperature, the reaction mixture was poured into ice-water (160 ml) and extracted with ethyl acetate. The extract was washed with a saturated sodium chloride solution and dried over magnesium sulfate. The solvent was evaporated to give syrup of 1-[2-{5-[3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl]-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine (1.97 g). See Example 2-(11).

IR (Nujol) : 3300, 1650, 1610, 1580, 1125, 990, 960, 845, 745 cm⁻¹

Claims

Claims for the following Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula :



wherein

R¹ is phenyl substituted with substituent(s) selected from the group consisting of hydroxy, C₁-C₈ alkoxy(C₁-C₈)alkoxy-(C₁-C₈)alkoxy, C₁-C₈ alkyl, C₁-C₈ alkanoyloxy, C₁-C₈ alkoxycarbonyloxy, halogen and C₁-C₈ alkoxy,

A is C₁-C₈ alkylene, and

B is vinylene, propenylene, butenylene, pentenylene, butadienylene or pentadienylene, and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein R¹ is phenyl substituted with mono-, or dihydroxy and mono-, or di(C₁-C₈)alkoxy.

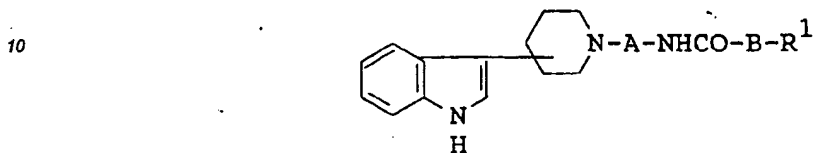
3. A compound of claim 2, which is 1-[2-{5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine.

4. A compound of claim 1, wherein R¹ is phenyl substituted with mono, or di(C₁-C₆)-alkanoyloxy and mono-, or di(C₁-C₆)alkoxy, or with mono-, or di(C₁-C₆)alkoxycarbonyloxy and mono-, or di(C₁-C₆)alkoxy.

5. A compound of claim 4, which is 1-[2-{5-(4-acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine.

5 6. A compound of claim 4, which is 1-[2-{5-(4-ethoxycarbonyloxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)-piperidine.

7. A process for preparing a compound of the formula :



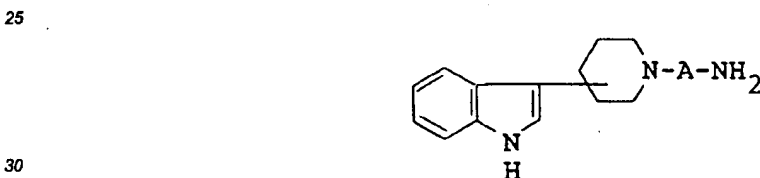
15 wherein

R¹ is phenyl substituted with substituent(s) selected from the group consisting of hydroxy, C₁-C₆ alkoxy(C₁-C₆)alkoxy-(C₁-C₆)alkoxy, C₁-C₆ alkyl, C₁-C₆ alkanoyloxy, C₁-C₆ alkoxycarbonyloxy, halogen and C₁-C₆ alkoxy,

20 A is C₁-C₆ alkylene, and

B is vinylene, propenylene, butenylene, pentenylene, butadienylene or pentadienylene, or its salt, which comprises

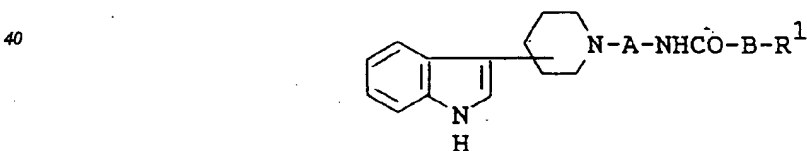
a) reacting a compound of the formula :



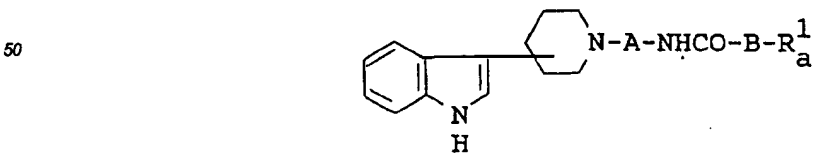
wherein A is as defined above, or its reactive derivative at the amino group or a salt thereof with a compound of the formula :

35 R¹-B-COOH

wherein R¹ and B are each as defined above, or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula :



wherein R¹, A and B are each as defined above, or its salt, or
b) subjecting a compound of the formula :

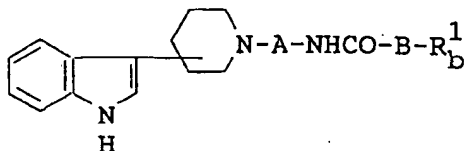


wherein

R_a¹ is phenyl substituted with C₁-C₆ alkoxy-(C₁-C₆)alkoxy(C₁-C₆)alkoxy, with C₁-C₆ alkoxy(C₁-C₆)al-

koxy(C₁-C₆)alkoxy and halogen, with C₁-C₆ alkoxy(C₁-C₆)-alkoxy(C₁-C₆)alkoxy and C₁-C₆ alkyl, or with C₁-C₆ alkoxy(C₁-C₆)alkoxy-(C₁-C₆)alkoxy and C₁-C₆ alkoxy, and

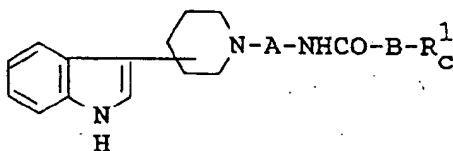
A and B are each as defined above, or its salt to elimination reaction of C₁-C₆ alkoxy-(C₁-C₆)alkoxy(C₁-C₆)alkyl to give a compound of the formula :



wherein

R_D¹ is phenyl substituted with hydroxy, with hydroxy and halogen, with hydroxy and C₁-C₆ alkyl, or with hydroxy and C₁-C₆ alkoxy, and

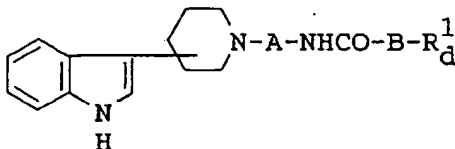
A and B are each as defined above, or its salt, or
c) acylating a compound of the formula :



wherein

R_C¹ is phenyl substituted with hydroxy, or with hydroxy and C₁-C₆ alkoxy, and

A and B are each as defined above, or its salt to give a compound of the formula :



wherein

R_d¹ is phenyl substituted with C₁-C₆ alkoxy-carbonyloxy, or with acyloxy selected from C₁-C₆ alkanoyloxy and C₁-C₆ alkoxycarbonyloxy and C₁-C₆ alkoxy, and

A and B are each as defined above, or its salt.

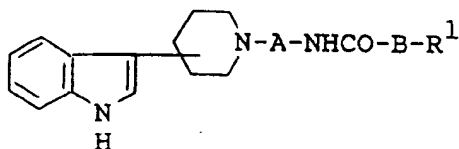
8. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.

9. A compound of claim 1 for use as a medicament.

10. Use of a compound of claim 1 and a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of allergic disease in human beings or animals.

Claims for the following Contracting State: ES

1. A process for preparing a compound of the formula :



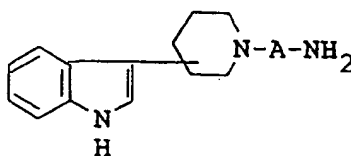
wherein

R¹ is phenyl substituted with substituent(s) selected from the group consisting of hydroxy, C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, C₁-C₆ alkyl, C₁-C₆ alkanoyloxy, C₁-C₆ alkoxycarbonyloxy, halogen and C₁-C₆ alkoxy,

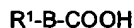
A is C₁-C₆ alkylene, and

B is vinylene, propenylene, butenylene, pentenylene, butadienylene or pentadienylene, or its salt, which comprises

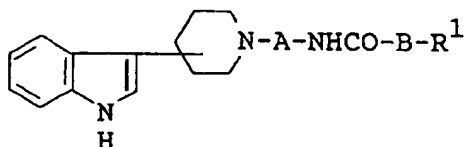
a) reacting a compound of the formula :



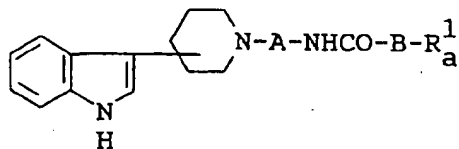
wherein A is as defined above,
or its reactive derivative at the amino group
or a salt thereof with a compound of the formula :



wherein R¹ and B are each as defined above,
or its reactive derivative at the carboxy group
or a salt thereof to give a compound of the formula :



wherein R¹, A and B are each as defined above, or its salt, or
b) subjecting a compound of the formula :



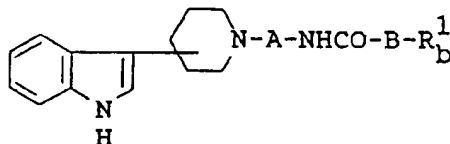
wherein

R_a¹ is phenyl substituted with C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, with C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy and halogen, with C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy and C₁-C₆ alkyl, or with C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy and C₁-C₆ alkoxy, and

A and B are each as defined above,
or its salt to elimination reaction of C₁-C₆ alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkyl to give a compound of the for-

mula :

5



10

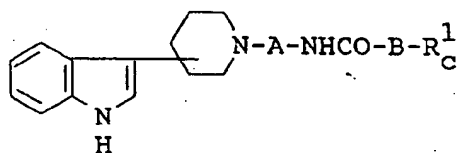
wherein

R_D^1 is phenyl substituted with hydroxy, with hydroxy and halogen, with hydroxy and C_1-C_6 alkyl, or with hydroxy and C_1-C_6 alkoxy, and

A and B are each as defined above, or its salt, or

c) acylating a compound of the formula :

15



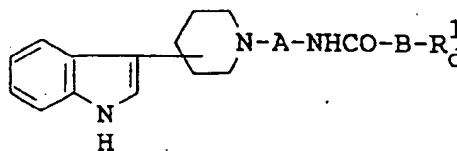
20

wherein

R_C^1 is phenyl substituted with hydroxy, or with hydroxy and C_1-C_6 alkoxy, and

A and B are each as defined above, or its salt to give a compound of the formula :

25



30

wherein

R_d^1 is phenyl substituted with C_1-C_6 alkoxycarbonyloxy, or with acyloxy selected from C_1-C_6 alkanoyloxy and C_1-C_6 alkoxycarbonyloxy and C_1-C_6 alkoxy, and

A and B are each as defined above, or its salt.

35

2. A process of claim 1, wherein

R^1 is phenyl substituted with mono-, or dihydroxy and mono-, or di(C_1-C_6)alkoxy.

40

3. A process of claim 2 for preparing 1-[2-{5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine.

4. A process of claim 1, wherein

R^1 is phenyl substituted with mono-, or di(C_1-C_6)alkanoyloxy and mono-, or di(C_1-C_6)alkoxy, or with mono-, or di(C_1-C_6)alkoxycarbonyloxy and mono-, or di(C_1-C_6)alkoxy.

45

5. A process of claim 4 for preparing 1-[2-{5-(4-acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidine.

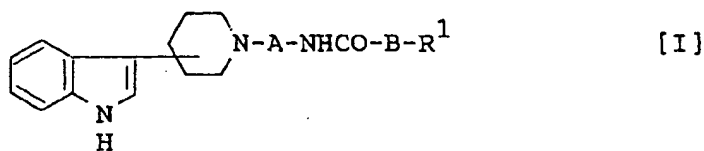
6. A process of claim 4 for preparing 1-[2-{5-(4-ethoxycarbonyloxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)-piperidine.

50

Claims for the following Contracting State: GR

1. A process for preparing a compound of the formula [I]:

55



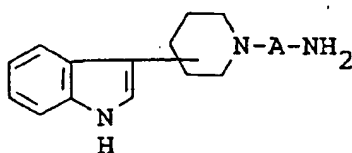
wherein

R¹ is phenyl substituted with substituent(s) selected from the group consisting of hydroxy, C₁-C₈ alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy, C₁-C₈ alkyl, C₁-C₈ alkanoyloxy, C₁-C₈ alkoxycarbonyloxy, halogen and C₁-C₈ alkoxy,

A is C₁-C₈ alkylene, and

B is vinylene, propenylene, butenylene, pentenylene, butadienylene or pentadienylene, or its salt which comprises

a) reacting a compound of the formula :



wherein A is as defined above,

or its reactive derivative at the amino group

or a salt thereof with a compound of the formula :

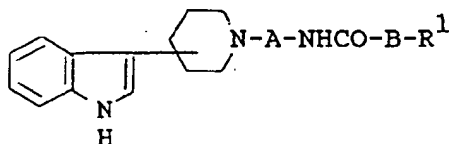


wherein

R¹ and B are each as defined above,

or its reactive derivative at the carboxy group

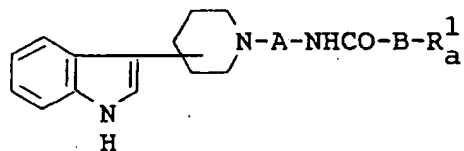
or a salt thereof to give a compound of the formula :



wherein

R¹, A and B are each as defined above, or its salt, or

b) subjecting a compound of the formula :

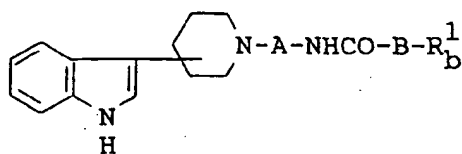


wherein

R_a¹ is phenyl substituted with C₁-C₈ alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy, with C₁-C₈ alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy and halogen, with C₁-C₈ alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy and C₁-C₈ alkyl, or with C₁-C₈ alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy and C₁-C₈ alkoxy, and

A and B are each as defined above,

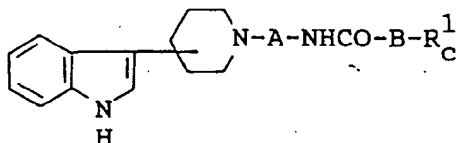
or its salt to elimination reaction of C₁-C₈ alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkyl to give a compound of the formula :



wherein

R_b^1 is phenyl substituted with hydroxy, with hydroxy and halogen, with hydroxy and C_1-C_6 alkyl, or with hydroxy and C_1-C_6 alkoxy, and

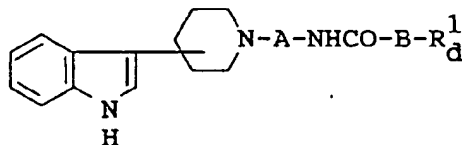
A and B are each as defined above, or its salt, or c) acylating a compound of the formula :



wherein

R_c^1 is phenyl substituted with hydroxy, or with hydroxy and C_1-C_6 alkoxy, and

A and B are each as defined above, or its salt to give a compound of the formula :



wherein

R_d^1 is phenyl substituted with C_1-C_6 alkoxycarbonyloxy, or with acyloxy selected from C_1-C_6 alkanoyloxy and C_1-C_6 alkoxycarbonyloxy and C_1-C_6 alkoxy, and

A and B are each as defined above, or its salt.

2. A process of claim 1, wherein

R^1 is phenyl substituted with mono-, or dihydroxy and mono-, or di(C_1-C_6)alkoxy.

3. A process of claim 2 for preparing 1-[2-{5-(4-hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine.

4. A process of claim 1, wherein

R^1 is phenyl substituted with mono-, or di(C_1-C_6)alkanoyloxy and mono-, or di(C_1-C_6)alkoxy, or with mono-, or di(C_1-C_6)alkoxycarbonyloxy and mono-, or di(C_1-C_6)alkoxy.

5. A process of claim 4 for preparing 1-[2-{5-(4-acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine.

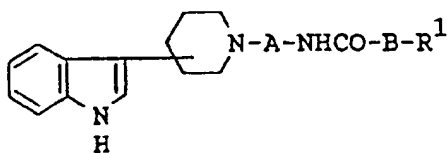
6. A process of claim 4 for preparing 1-[2-{5-(4-ethoxycarbonyloxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidine.

7. Modification of the process claimed in claim 1 which is characterised by bringing a compound of formula I, or a non-toxic salt thereof, produced by a process claimed in claim 1, into pharmaceutically acceptable form by admixture or presentation of said compound with a pharmaceutically acceptable diluent or carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



5

worin bedeuten:

R¹ Phenyl, das substituiert ist durch einen oder mehr Substituenten, ausgewählt aus der Gruppe, die besteht aus Hydroxy, C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, C₁-C₆-Alkyl, C₁-C₆-Alkanoyloxy, C₁-C₆-Alkoxy-carbonyloxy, Halogen und C₁-C₆-Alkoxy,

A C₁-C₆-Alkylen und

B Vinylen, Propenylen, Butenylen, Pentenylen, Butadienylen oder Pentadienylen,

und ein pharmazeutisch akzeptables Salz derselben.

2. Verbindung nach Anspruch 1, in der R¹ steht für Phenyl, das substituiert ist durch Mono- oder Dihydroxy- und Mono- oder Di(C₁-C₆)alkoxy.

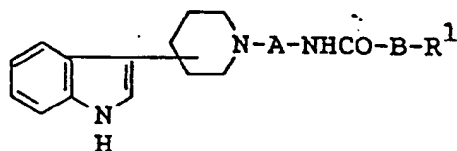
3. Verbindung nach Anspruch 2, bei der es sich handelt um 1-[2-{5-(4-Hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidin.

4. Verbindung nach Anspruch 1, bei der R¹ steht für Phenyl, das substituiert ist durch Mono- oder Di(C₁-C₆)alkanoyloxy und Mono- oder Di(C₁-C₆)alkoxy oder durch Mono- oder Di(C₁-C₆)alkoxycarbonyloxy und Mono- oder Di(C₁-C₆)alkoxy.

5. Verbindung nach Anspruch 4, bei der es sich handelt um 1-[2-{5-(4-Acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidin.

9. Verbindung nach Anspruch 4, bei der es sich handelt um 1-[2-{5-(4-Ethoxycarbonyloxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)piperidin.

7. Verfahren zur Herstellung einer Verbindung der Formel



30

35 worin bedeuten:

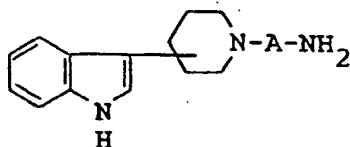
R¹ Phenyl, das substituiert ist durch einen oder mehr Substituenten, ausgewählt aus der Gruppe, die besteht aus Hydroxy, C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, C₁-C₆-Alkyl, C₁-C₆-Alkanoyloxy, C₁-C₆-Alkoxy-carbonyloxy, Halogen und C₁-C₆-Alkoxy,

A C₁-C₆-Alkylen und

40 B Vinylen, Propenylen, Butenylen, Pentenylen, Butadienylen oder Pentadienylen,

oder ihres Salzes, das umfaßt

a) die Umsetzung einer Verbindung der Formel



45

50 worin A wie oben definiert ist,

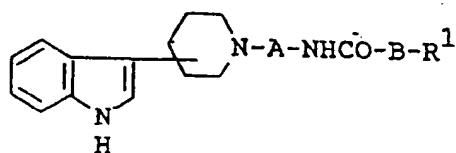
oder ihres reaktionsfähigen Derivats an der Aminogruppe oder eines Salzes desselben mit einer Verbindung der Formel



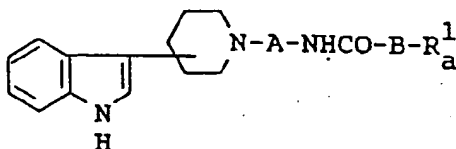
55 worin R¹ und B jeweils wie oben definiert sind,

oder ihrem reaktionsfähigen Derivat an der Carboxygruppe

oder einem Salz derselben unter Bildung einer Verbindung der Formel

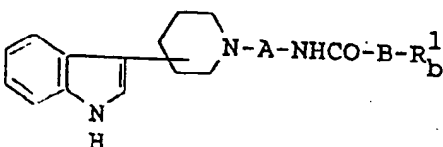


worin R¹, A und B jeweils wie oben definiert sind, oder ihres Salzes; oder
b) die Durchführung einer Reaktion zur Entfernung von C₁-C₈-Alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkyl aus einer Verbindung der Formel



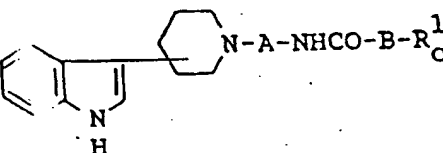
worin

R¹ₐ steht für Phenyl, das substituiert ist durch C₁-C₈-Alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy, durch C₁-C₈-Alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy und Halogen, durch C₁-C₈-Alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy und C₁-C₈-Alkyl oder durch C₁-C₈-Alkoxy(C₁-C₈)alkoxy(C₁-C₈)alkoxy und C₁-C₈-Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihrem Salz unter Bildung einer Verbindung der Formel



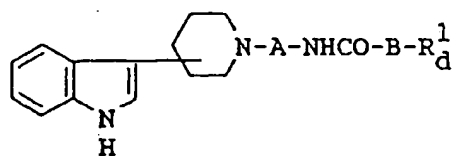
worin

R¹ᵇ steht für Phenyl, das substituiert ist durch Hydroxy, durch Hydroxy und Halogen, durch Hydroxy und C₁-C₈-Alkyl oder durch Hydroxy und C₁-C₈-Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes; oder
c) durch Acylierung einer Verbindung der Formel



worin

R¹ᶜ steht für Phenyl, das substituiert ist durch Hydroxy oder durch Hydroxy und C₁-C₈-Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes unter Bildung einer Verbindung der Formel



worin

R¹ᵈ steht für Phenyl, das substituiert ist durch C₁-C₈-Alkoxy-carbonyloxy oder durch Acyloxy, ausgewählt aus C₁-C₈-Alkanoyloxy und C₁-C₈-Alkoxy-carbonyloxy und C₁-C₈-Alkoxy und worin A und B jeweils

wie oben definiert sind, oder ihres Salzes.

8. Pharmazeutische Zusammensetzung, die eine Verbindung nach Anspruch 1 als aktiven Bestandteil (Wirkstoff) in Assoziation mit einem pharmazeutisch akzeptablen, im wesentlichen nicht-toxischen Träger oder Exzipienten enthält.

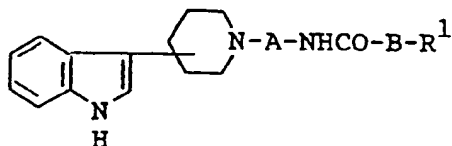
9. Verbindung nach Anspruch 1 für die Verwendung als Arzneimittel.

10. Verwendung einer Verbindung nach Anspruch 1 und eines pharmazeutisch akzeptablen Salzes derselben für die Herstellung eines Arzneimittels für die Behandlung einer allergischen Erkrankung bei Menschen oder Tieren.

10 Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel

15



20

worin bedeuten:

R¹ Phenyl, das substituiert ist durch einen oder mehr Substituenten, ausgewählt aus der Gruppe, die besteht aus Hydroxy, C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, C₁-C₆-Alkyl, C₁-C₆-Alkanoyloxy, C₁-C₆-Alkoxy-carbonyloxy, Halogen und C₁-C₆-Alkoxy,

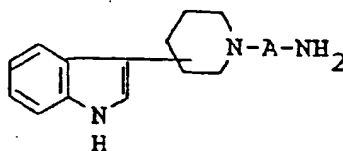
25

A C₁-C₆-Alkylen und

B Vinylen, Propenylen, Butenylen, Pentenylen, Butadienylen oder Pentadienylen, oder ihres Salzes, das umfaßt

a) die Umsetzung einer Verbindung der Formel

30



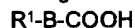
35

worin A wie oben definiert ist,

oder ihres reaktionsfähigen Derivats an der Aminogruppe

oder eines Salzes derselben mit einer Verbindung der Formel

40

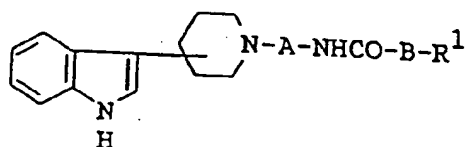


worin R¹ und B jeweils wie oben definiert sind,

oder ihrem reaktionsfähigen Derivat an der Carboxygruppe

oder einem Salz derselben unter Bildung einer Verbindung der Formel

45

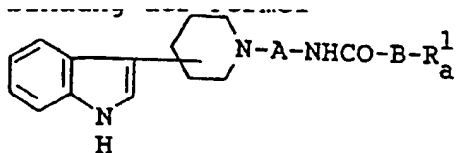


50

worin R¹, A und B jeweils wie oben definiert sind, oder eines Salzes derselben; oder

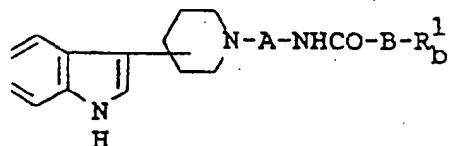
b) die Eliminierung von C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkyl aus einer Verbindung der Formel

55



worin

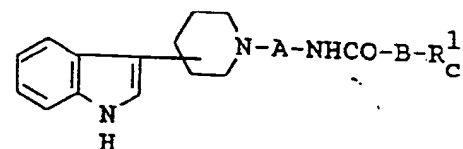
R_a^1 steht für Phenyl, das substituiert ist durch C_1 - C_6 -Alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy, durch C_1 - C_6 -Alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy und Halogen, durch C_1 - C_6 -Alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy und C_1 - C_6 -Alkyl oder durch C_1 - C_6 -Alkoxy(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy und C_1 - C_6 -Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihrem Salz unter Bildung einer Verbindung der Formel



worin

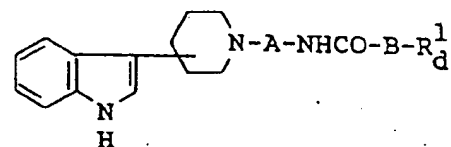
R_b^1 steht für Phenyl, das substituiert ist durch Hydroxy, durch Hydroxy und Halogen, durch Hydroxy und C_1 - C_6 -Alkyl oder durch Hydroxy und C_1 - C_6 -Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes; oder

c) die Acylierung einer Verbindung der Formel



worin

R_c^1 steht für Phenyl, das substituiert ist durch Hydroxy oder durch Hydroxy und C_1 - C_6 -Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes unter Bildung einer Verbindung der Formel



worin

R_d^1 steht für Phenyl, das substituiert ist durch C_1 - C_6 -Alkoxycarbonyloxy oder durch Acyloxy, ausgewählt aus C_1 - C_6 -Alkanoyloxy und C_1 - C_6 -Alkoxycarbonyloxy und C_1 - C_6 -Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes.

2. Verfahren nach Anspruch 1, worin R^1 steht für Phenyl, das substituiert ist durch Mono- oder Dihydroxy- und Mono- oder Di(C_1 - C_6)alkoxy.

3. Verfahren nach Anspruch 2, zur Herstellung der Verbindung 1-[2-{5-(4-Hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidin.

4. Verfahren nach Anspruch 1, worin R^1 steht für Phenyl, das substituiert ist durch Mono- oder Di(C_1 - C_6)alkanoyloxy und Mono- oder Di(C_1 - C_6)alkoxy oder durch Mono- oder Di(C_1 - C_6)alkoxycarbonyloxy und Mono- oder Di(C_1 - C_6)alkoxy.

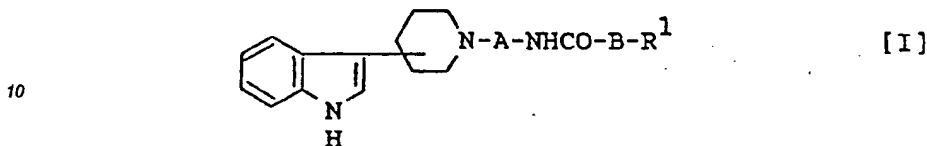
5. Verfahren nach Anspruch 4 zur Herstellung von 1-[2-{5-(4-Acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienoylamino}ethyl]-4-(3-indolyl)piperidin.

6. Verfahren nach Anspruch 4 zur Herstellung von 1-[2-{5-(4-Ethoxycarbonyloxy-3,5-dimethoxyphenyl)-

(2E,4E)-2,4-pentadienylamino}ethyl]-4-(3-indolyl)-piperidin.

Patentansprüche für folgende Vertragsstaat: GR

5 1. Verfahren zur Herstellung einer Verbindung der Formel



worin bedeuten:

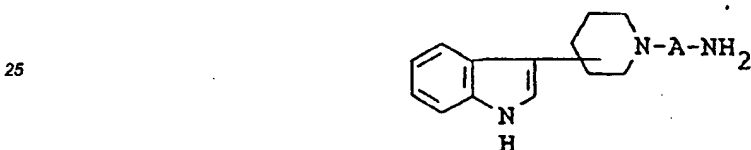
15 R¹ Phenyl, das substituiert ist durch einen oder mehr Substituenten, ausgewählt aus der Gruppe, die besteht aus Hydroxy, C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, C₁-C₆-Alkyl, C₁-C₆-Alkanoyloxy, C₁-C₆-Alkoxy-carbonyloxy, Halogen und C₁-C₆-Alkoxy,

A C₁-C₆-Alkylen und

B Vinylen, Propenylen, Butenylen, Pentenylen, Butadienylen oder Pentadienylen,

20 oder ihres Salzes, das umfaßt

a) die Umsetzung einer Verbindung der Formel



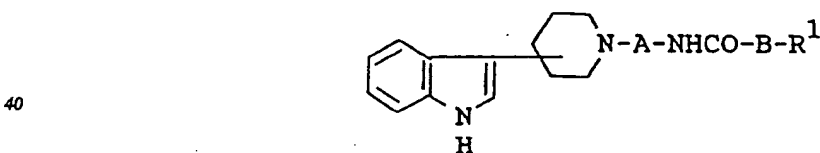
30 worin A wie oben definiert ist,

oder ihres reaktionsfähigen Derivats an der Aminogruppe

oder eines Salzes derselben mit einer Verbindung der Formel

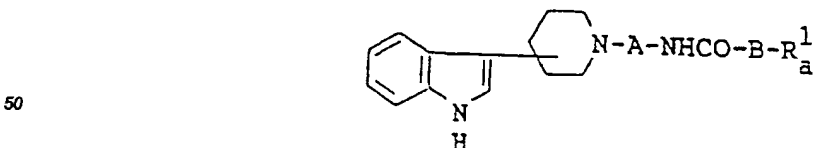
R¹-B-COOH

35 worin R¹ und B jeweils wie oben definiert sind, oder ihrem reaktionsfähigen Derivat an der Carboxygruppe oder einem Salz derselben unter Bildung einer Verbindung der Formel

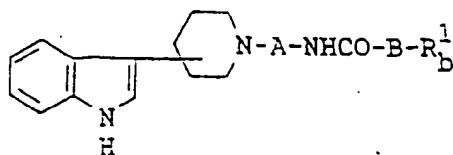


45 worin R¹, A und B jeweils wie oben definiert sind, oder eines Salzes derselben; oder

b) die Eliminierung von C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-

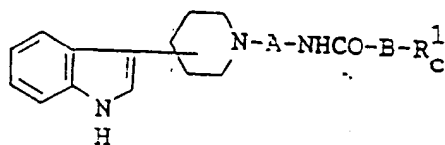


55 C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy, durch C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy und Halogen, durch C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy und C₁-C₆-Alkyl oder durch C₁-C₆-Alkoxy(C₁-C₆)alkoxy(C₁-C₆)alkoxy und C₁-C₆-Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihrem Salz unter Bildung einer Verbindung der Formel

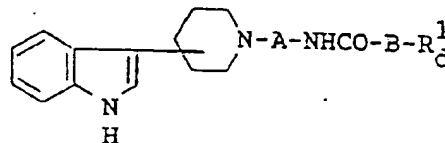


worin R_D^1 steht für Phenyl, das substituiert ist durch Hydroxy, durch Hydroxy und Halogen, durch Hydroxy und C_1 - C_6 -Alkyl oder durch Hydroxy und C_1 - C_6 -Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes; oder

c) die Acylierung einer Verbindung der Formel



worin R_C^1 steht für Phenyl, das substituiert ist durch Hydroxy oder durch Hydroxy und C_1 - C_6 -Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes unter Bildung einer Verbindung der Formel



worin R_d^1 steht für Phenyl, das substituiert ist durch C_1 - C_6 -Alkoxy-carbonyloxy oder durch Acyloxy, ausgewählt aus C_1 - C_6 -Alkanoyloxy und C_1 - C_6 -Alkoxy-carbonyloxy und C_1 - C_6 -Alkoxy und worin A und B jeweils wie oben definiert sind, oder ihres Salzes.

2. Verfahren nach Anspruch 1, worin R^1 steht für Phenyl, das substituiert ist durch Mono- oder Dihydroxy- und Mono- oder Di(C_1 - C_6)alkoxy.

3. Verfahren nach Anspruch 2, zur Herstellung der Verbindung 1-(2-{5-(4-Hydroxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl)-4-(3-indolyl)piperidin.

4. Verfahren nach Anspruch 1, worin R^1 steht für Phenyl, das substituiert ist durch Mono- oder Di(C_1 - C_6)alkanoyloxy und Mono- oder Di(C_1 - C_6)alkoxy oder durch Mono- oder Di(C_1 - C_6)alkoxy-carbonyloxy und Mono- oder Di(C_1 - C_6)alkoxy.

5. Verfahren nach Anspruch 4 zur Herstellung von 1-(2-{5-(4-Acetoxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl)-4-(3-indolyl)piperidin.

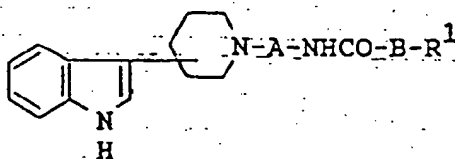
6. Verfahren nach Anspruch 4 zur Herstellung von 1-(2-{5-(4-Ethoxycarbonyloxy-3,5-dimethoxyphenyl)-(2E,4E)-2,4-pentadienylamino}ethyl)-4-(3-indolyl)piperidin.

7. Modifizierung des Verfahrens nach Anspruch 1, das dadurch gekennzeichnet ist, daß man eine Verbindung der Formel (I) oder ein nicht-toxisches Salz derselben, hergestellt nach dem Verfahren nach Anspruch 1, in eine pharmazeutisch akzeptable Form überführt durch Mischen oder Präsentieren dieser Verbindung mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger.

Revendications

Revendications pour les Etats Contractants suivants: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé répondant à la formule



5

dans laquelle

R¹ est un groupe phényle substitué par un ou plusieurs substituants choisis parmi les groupes hydroxy, (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆), alkyle en C₁ à C₆, alcanoyloxy en C₁ à C₆, (alcoxy en C₁ à C₆)carbonyloxy, par un atome d'halogène et par un groupe alcoxy en C₁ à C₆,

A est un groupe alkylène en C₁ à C₆, et

B est un groupe vinylène, propénylène, buténylène, penténylène, butadiénylène ou pentadiénylène, ou un de ses sels pharmaceutiquement acceptable.

2. Composé selon la revendication 1, dans lequel : R¹ est un groupe phényle substitué par un ou deux groupes hydroxy et par un ou deux groupes alcoxy en C₁ à C₆.

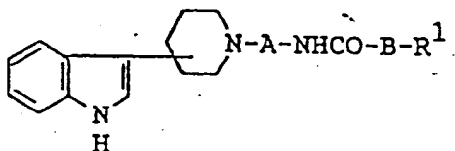
3. Composé selon la revendication 2 qui est la 1-[2-{5-(4-hydroxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino)éthyl]-4-(3-indolyl)pipéridine,

4. Composé selon la revendication 1, dans lequel : R¹ est un groupe phényle substitué par un ou deux groupes alcanoyloxy en C₁ à C₆ et par un ou deux groupes alcoxy en C₁ à C₆, ou par un ou deux groupes (alcoxy en C₁ à C₆)carbonyloxy et par un ou deux groupes alcoxy en C₁ à C₆.

5. Composé selon la revendication 4, qui est la 1-[2-{5-(4-acétoxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino)éthyl]-4-(3-indolyl)pipéridine,

6. Composé selon la revendication 4, qui est la 1-[2-{5-(4-éthoxycarbonyloxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino)éthyl]-4-(3-indolyl)pipéridine.

7. Procédé de préparation d'un composé répondant à la formule :



30

35

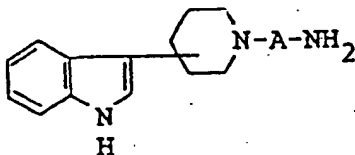
dans laquelle

R¹ est un groupe phényle substitué par un ou plusieurs substituants choisis parmi les groupes hydroxy, (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆), alkyle en C₁ à C₆, alcanoyloxy en C₁ à C₆, (alcoxy en C₁ à C₆)carbonyloxy, par un atome d'halogène et par un groupe alcoxy en C₁ à C₆,

A est un groupe alkylène en C₁ à C₆, et

B est un groupe vinylène, propénylène, buténylène, penténylène, butadiénylène ou pentadiénylène, ou un de ses sels, qui comprend

a) le fait de faire réagir un composé répondant à la formule :



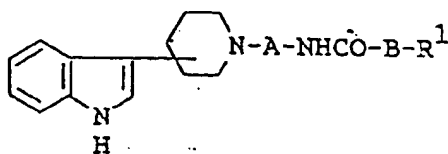
45

50

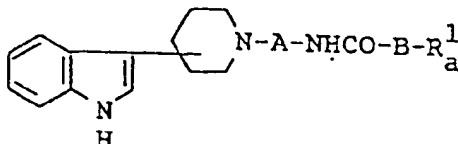
dans laquelle A est tel que défini ci-dessus, ou un de ses dérivés réactifs sur le groupe amino ou un de ses sels avec un composé répondant à la formule:



dans laquelle R¹ et B sont chacun tels que définis ci-dessus, ou un de ses dérivés réactifs sur le groupe carboxy ou un de ses sels, pour donner un composé répondant à la formule :



dans laquelle R¹, A et B sont chacun tels que définis ci-dessus, ou un de ses sels, ou
b) le fait de soumettre un composé répondant à la formule :

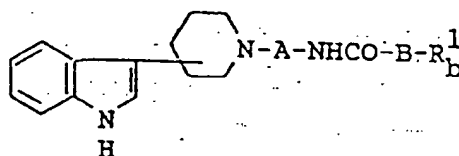


dans laquelle

R¹ₐ est un groupe phényle substitué par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆), par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et un atome d'halogène, par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et par un groupe alkyle en C₁ à C₆ ou par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels, à une réaction d'élimination du groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alkyle en C₁ à C₆) pour donner un composé répondant à la formule :

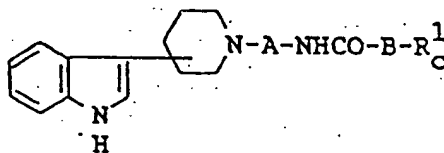


dans laquelle R¹ₐ est un groupe phényle substitué par un groupe hydroxy, par un groupe hydroxy et un atome d'halogène, par un groupe hydroxy et un groupe alkyle en C₁ à C₆, ou par un groupe hydroxy et par un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels, ou

c) le fait d'acyler un composé répondant à la formule:

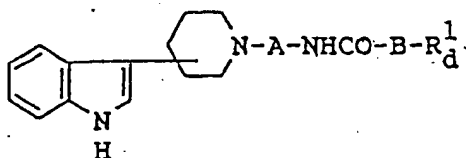


dans laquelle

R¹ₐ est un groupe phényle substitué par un groupe hydroxy, ou par un groupe hydroxy et un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels pour donner un composé répondant à la formule :



dans laquelle

R_d^1 est un groupe phényle substitué par un groupe (alcoxy en C_1 à C_6)carbonyloxy, ou par un groupe acyloxy choisi parmi un groupe alcanoyloxy en C_1 à C_6 et un groupe (alcoxy en C_1 à C_6)carbonyloxy et par un groupe alcoxy en C_1 à C_6 , et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels

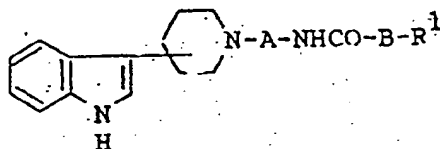
8. Composition pharmaceutique comprenant un composé selon la revendication 1, comme ingrédient actif, en association avec un support ou un excipient pharmaceutiquement acceptable, pratiquement non toxique.

9. Composé selon la revendication 1, pour emploi comme médicament.

10. Emploi d'un composé selon la revendication 1, de son sel pharmaceutiquement acceptable pour la fabrication d'un médicament pour le traitement des allergies chez les êtres humains ou les animaux.

Revendications pour l'Etat Contractant suivant: ES

1. Procédé de préparation d'un composé répondant à la formule :



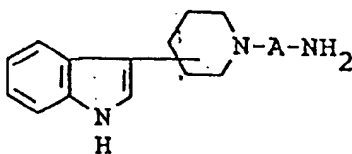
dans laquelle

R^1 est un groupe phényle substitué par un ou plusieurs substituants choisis parmi les groupes hydroxy, (alcoxy en C_1 à C_6) (alcoxy en C_1 à C_6)(alcoxy en C_1 à C_6), alkyle en C_1 à C_6 , alcanoyloxy en C_1 à C_6 , (alcoxy en C_1 à C_6)carbonyloxy, par un atome d'halogène et par un groupe alcoxy en C_1 à C_6 , et

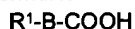
A est un groupe alkylène en C_1 à C_6 , et

B est un groupe vinyène, propénylène, buténylène, penténylène, butadiénylène ou pentadiénylène, ou un de ses sels, qui comprend

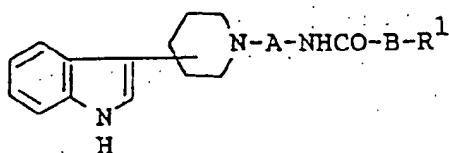
a) le fait de faire réagir un composé répondant à la formule :



dans laquelle A est tel que défini ci-dessus, ou un de ses dérivés réactifs sur le groupe amino ou un de ses sels avec un composé répondant à la formule:

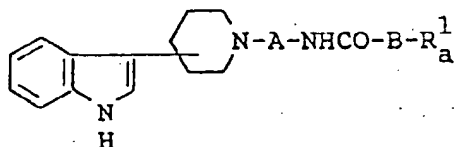


dans laquelle R^1 et B sont chacun tels que définis ci-dessus, ou un de ses dérivés réactifs sur le groupe carboxy ou un de ses sels, pour donner un composé répondant à la formule :



dans laquelle R¹, A et B sont chacun tels que définis ci-dessus,
ou un de ses sels, ou

b) le fait de soumettre un composé répondant à la formule :

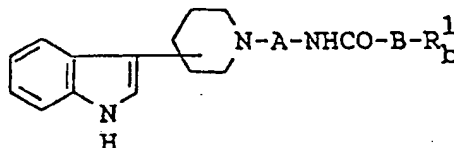


dans laquelle

R¹ₐ est un groupe phényle substitué par un groupe {alcoxy en C₁ à C₆} (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆), par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et un atome d'halogène, par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et un groupe alkyle en C₁ à C₆ ou par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et par un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels, à une réaction d'élimination du groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alkyle en C₁ à C₆) pour donner un composé répondant à la formule :



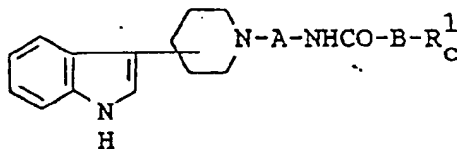
dans laquelle

R¹ₑ est un groupe phényle substitué par un groupe hydroxy, par un groupe hydroxy et un atome d'halogène, par un groupe hydroxy et un groupe alkyle en C₁ à C₆, ou par un groupe hydroxy et par un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels, ou

c) le fait d'acyler un composé répondant à la formule :

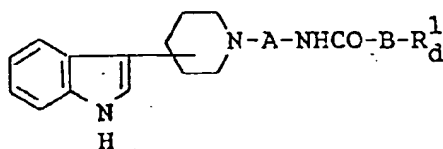


dans laquelle

R¹ₑ est un groupe phényle substitué par un hydroxy et un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels pour donner un composé répondant à la formule :



dans laquelle

R_d^1 est un groupe phényle substitué par un groupe (alcoxy en C_1 à C_6)carboxyloxy ou par un groupe acyloxy choisi parmi un groupe alcanoyloxy en C_1 à C_6 et un groupe (alcoxy en C_1 à C_6)carboxyloxy et par un groupe alcoxy en C_1 à C_6 , et

A et B sont chacun tels que définis ci-dessus,

ou un de ses sels

2. Procédé selon la revendication 1, dans lequel : R^1 est un groupe phényle substitué par un ou deux groupes hydroxy et par un ou deux groupes alcoxy en C_1 à C_6 .

3. Procédé selon la revendication 2 pour préparer la 1-[2-{5-(4-hydroxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino)éthyl]-4-(3-indolyl)pipéridine.

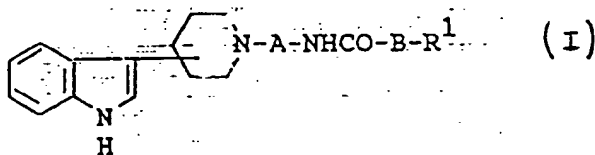
4. Procédé selon la revendication 1, dans lequel : R^1 est un groupe phényle substitué par un ou deux groupes alcanoyloxy en C_1 à C_6 et un ou deux groupes alcoxy en C_1 à C_6 ou par un ou deux groupes (alcoxy en C_1 à C_6)carboxyloxy et par un ou deux groupes alcoxy en C_1 à C_6 .

5. Procédé selon la revendication 4, pour préparer la 1-[2-{5-(4-acétoxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino)éthyl]-4-(3-indolyl)pipéridine.

6. Procédé selon la revendication 4, pour préparer la 1-[2-{5-(4-éthoxycarboxyloxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino)éthyl]-4-(3-indolyl)pipéridine.

Revendications pour l'Etat Contractant suivant: GB

1. Procédé de préparation d'un composé répondant à la formule [I] :



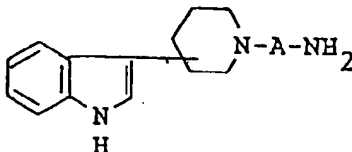
dans laquelle

R^1 est un groupe phényle substitué par un ou plusieurs substituants choisis parmi les groupes hydroxy, (alcoxy en C_1 à C_6) (alcoxy en C_1 à C_6)(alcoxy en C_1 à C_6), alkyle en C_1 à C_6 , alcanoyloxy en C_1 à C_6 , (alcoxy en C_1 à C_6)carboxyloxy, par un atome d'halogène et par un groupe alcoxy en C_1 à C_6 ,

A est un groupe alkylène en C_1 à C_6 , et

B est un groupe vinylène, propénylène, buténylène, penténylène, butadiénylène ou pentadiénylène, ou un de ses sels, qui comprend

a) le fait de faire réagir un composé répondant à la formule :

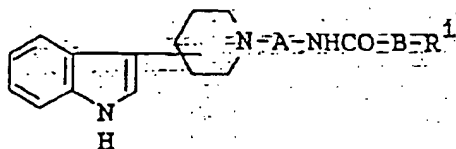


dans laquelle A est tel que défini ci-dessus, ou un de ses dérivés réactifs sur le groupe amino ou un de ses sels avec un composé répondant à la formule:



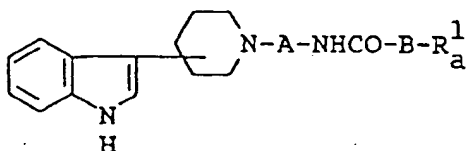
dans laquelle R^1 et B sont chacun tels que définis ci-dessus, ou un de ses dérivés réactifs sur le groupe

carboxy ou un de ses sels, pour donner un composé répondant à la formule :



10 dans laquelle R¹, A et B sont chacun tels que définis ci-dessus,
ou un de ses sels, ou

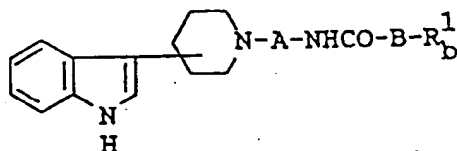
b) le fait de soumettre un composé répondant à la formule :



20 dans laquelle

R¹ₐ est un groupe phényle substitué par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆), par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et un atome d'halogène, par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et par un groupe alkyle en C₁ à C₆ ou par un groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) et un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,
ou un de ses sels, à une réaction d'élimination du groupe (alcoxy en C₁ à C₆) (alcoxy en C₁ à C₆) (alkyle en C₁ à C₆) pour donner un composé répondant à la formule :

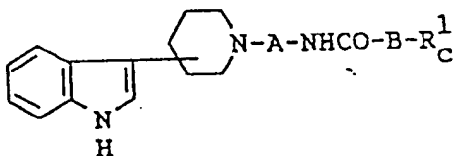


35 dans laquelle

R¹ₐ est un groupe phényle substitué par un groupe hydroxy, par un groupe hydroxy et un atome d'halogène, par un groupe hydroxy et un groupe alkyle en C₁ à C₆, ou par un groupe hydroxy et par un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,
ou un de ses sels, ou

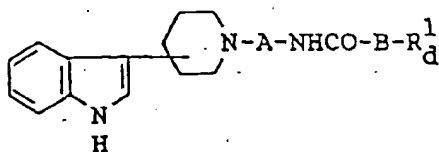
c) le fait d'acyler un composé répondant à la formule :



45 dans laquelle

R¹ₐ est un groupe phényle substitué par un groupe hydroxy, ou par un groupe hydroxy et un groupe alcoxy en C₁ à C₆, et

A et B sont chacun tels que définis ci-dessus,
ou un de ses sels pour donner un composé répondant à la formule:



dans laquelle

R_d^1 est un groupe phényle substitué par un groupe (alcoxy en C_1 à C_6)carbonyloxy, ou par un groupe acyloxy choisi parmi un groupe alcanoyloxy en C_1 à C_6 et un groupe (alcoxy en C_1 à C_6)carbonyloxy et par un groupe alcoxy en C_1 à C_6 , et

A et B sont chacun tels que définis ci-dessus, ou un de ses sels.

2. Procédé selon la revendication 1, dans lequel : R^1 est un groupe phényle substitué par un ou deux groupes hydroxy et par un ou deux groupes alcoxy en C_1 à C_6 .

3. Procédé selon la revendication 2 pour préparer la 1-[2-{5-(4-hydroxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino}éthyl]-4-(3-indolyl)pipéridine.

4. Procédé selon la revendication 1, dans lequel : R^1 est un groupe phényle substitué par un ou deux groupes alcanoyloxy en C_1 à C_6 et par un ou deux groupes alcoxy en C_1 à C_6 , ou par un ou deux groupes (alcoxy en C_1 à C_6)carbonyloxy et par un ou deux groupes alcoxy en C_1 à C_6 .

5. Procédé selon la revendication 4, pour préparer la 1-[2-{5-(4-acétoxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino}éthyl]-4-(3-indolyl)pipéridine.

6. Procédé selon la revendication 4, pour préparer la 1-[2-{5-(4-éthoxycarbonyloxy-3,5-diméthoxyphényl)-(2E,4E)-2,4-pentadiénoylamino}éthyl]-4-(3-indolyl)pipéridine.

7. Variante du procédé selon la revendication 1, caractérisée en ce qu'on amène un composé répondant à la formule 1, ou un de ses sels non toxiques, préparé par le procédé revendiqué dans la revendication 1, sous une forme pharmaceutiquement acceptable par mélange ou présentation de ce composé avec un diluant ou support pharmaceutiquement acceptable.